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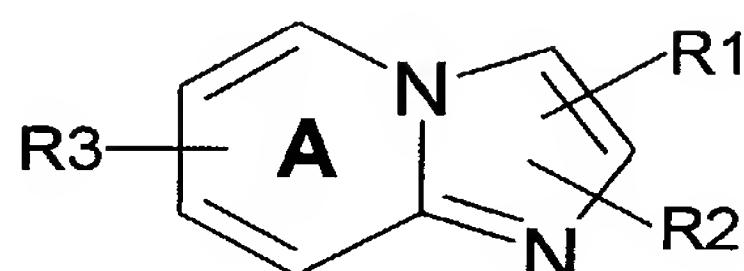
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A2

(54) Title: COMPOUNDS



(I)

(57) Abstract: The present invention relates to compounds of formula I which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a

method of therapeutic treatment using such a compound and processes for producing the compounds wherein: - R1, R2 and R3 are as defined in the description; and ring A is optionally further substituted.

WO 02/066477

COMPOUNDS

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

10 BACKGROUND TO THE INVENTION

Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

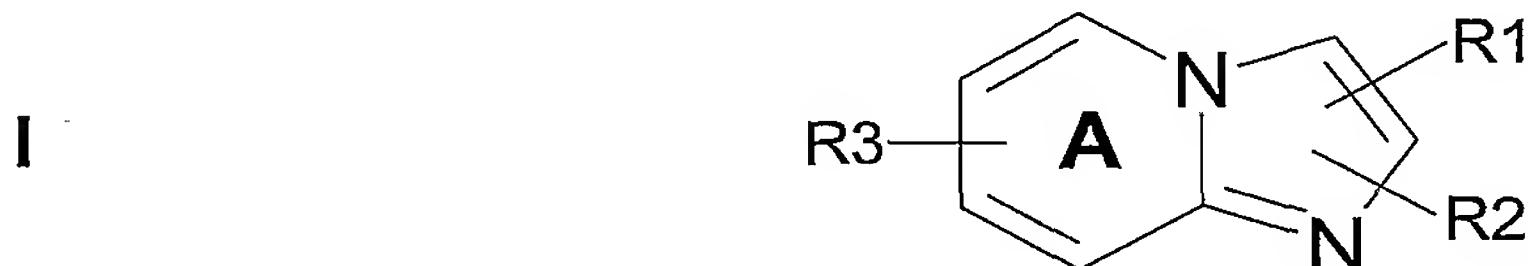
25 It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrope adenoma.

The following disclose compounds purported to act as GnRH antagonists: WO 97/44041, WO 98/5519, WO 99/51596 and WO 97/14697.

It would be desirable to provide further compounds, such compounds being GnRH
5 antagonists.

SUMMARY OF THE INVENTION

10 The present invention accordingly provides a compound of formula I or a pharmaceutically acceptable salt or solvate thereof



15 wherein:-

R1, R2 and R3 are independently selected from hydrogen and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom; and ring A is optionally further substituted.

20 The present invention also provides a pharmaceutical formulation comprising such a compound and a pharmaceutically acceptable diluent or carrier.

Furthermore, the present invention provides the following uses of the compound:-

25 (a) Use in the manufacture of a composition, for antagonising gonadotropin releasing hormone activity.

(b) Use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinising hormone by the pituitary gland of the patient.

5 (c) Use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

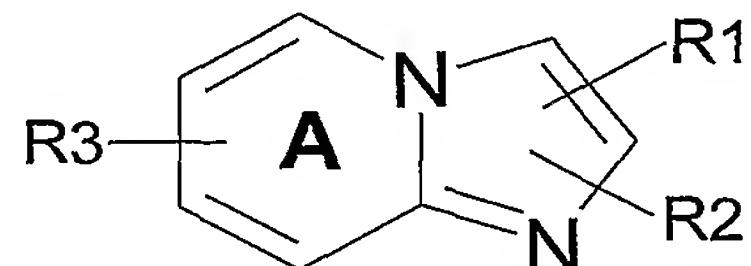
The present invention also relates to a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering the compound to the patient.

10 In addition, the invention provides a process of producing the compound.

DETAILED DESCRIPTION OF THE INVENTION

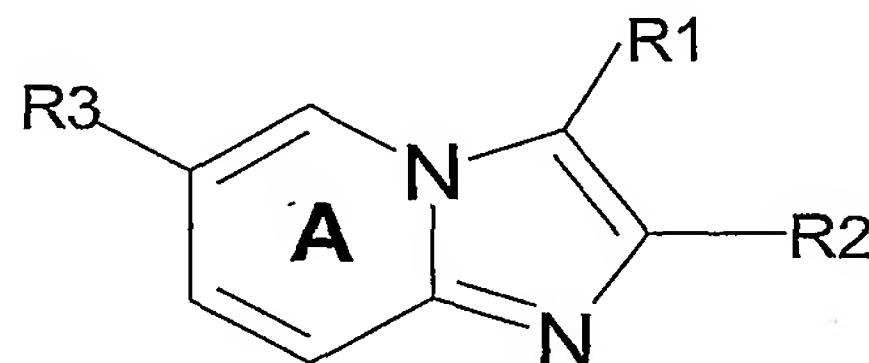
15 As discussed above, the present invention provides a compound of formula I or II or a pharmaceutically acceptable salt or solvate thereof

I



20

II



wherein:-

25 R1, R2 and R3 are independently selected from hydrogen and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom; and ring

A is optionally further substituted.

For definitions of preferred R1, R2 and R3 substituents, reference is made to WO 97/14697, where the definition of R¹ and R² in WO 97/14697 correspond with R1 and R2 respectively of the present invention, and the definition of R⁴ or R⁵ corresponds with R3 of the present invention. This disclosure of WO 97/14697, which provides disclosure of preferred R1, R2 and R3 substituents of the present invention, is explicitly incorporated herein by reference.

For further definitions of preferred R1, R2 and R3 substituents, reference is made to WO 95/28405, where the definition of R¹ and R² in WO 95/28405 correspond with R1 and R2 respectively of the present invention, and the definition of R⁴ or R⁵ corresponds with R3 of the present invention. This disclosure of WO 95/28405, which provides disclosure of preferred R1, R2 and R3 substituents of the present invention, is explicitly incorporated herein by reference.

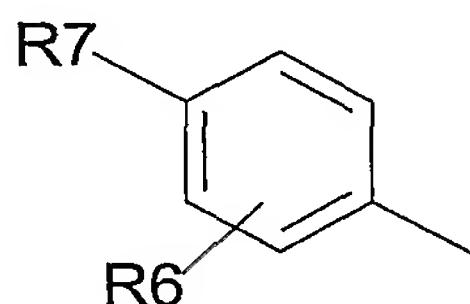
For yet further definitions of preferred R1, R2 and R3 substituents, reference is made to WO 97/40846, where the definition of R^{1a} and R^{2a} in WO 97/40846 correspond with R1 and R2 respectively of the present invention, and the definition of R^{3a}, R^{4a}, R^{5a} or R^{6a} corresponds with R3 of the present invention. In addition, the definition of R^{1e} and R^{2e} in WO 97/40846 correspond with R1 and R2 respectively of the present invention, and the definition of R^{3e}, R^{4e}, R^{5e} or R^{6e} corresponds with R3 of the present invention. This disclosure of WO 97/40846, which provides disclosure of preferred R1, R2 and R3 substituents of the present invention, is explicitly incorporated herein by reference.

Preferably, R1 and R2 are independently selected from a group of the formula R8-(CH₂)_b-, wherein each b independently represents zero or an integer from 1 to 5 and each R8 represents a group bonded through a nitrogen atom; a group of the formula R9-B'-, wherein R9 is an optionally substituted phenyl and B' is a chemical bond or spacer group; R10-(CH₂)_c-, wherein R10 is an optionally substituted amino and c is zero or an integer

from 1 to 5; an optionally substituted C₆ to C₁₄ aryl; an optionally substituted C₁ to C₂₀ hydrocarbon residue; and optionally substituted C₁ to C₆ alkyl. Alternative embodiments, having different R₁ and R₂ definitions are presented below.

- 5 Preferably, R₃ is selected from (CH₂)_a-R₄, wherein R₄ represents an optionally substituted C₆ to C₁₄ aryl (eg, phenyl) or an optionally substituted homo- or bi-cyclic heterocyclic ring (eg, a 5- or 6-membered mono-cyclic ring) and a represents zero or an integer from 1 to 5 (preferably, 1 or 2); a group bonded through a heteroatom (eg, where the heteroatom is O, N or S); an optionally substituted C₁ to C₂₀ hydrocarbon residue (eg, optionally substituted C₁ to C₆ alkyl or C₂ to C₁₂ alkenyl); optionally substituted C₁ to C₆ alkyl; C₁ to C₆ alkyl substituted with a group bonded through a sulphur atom; OR₅, wherein R₅ represents H or C₁ to C₆ alkyl; a carbonyl group optionally substituted with a hydrocarbon residue, the residue being optionally substituted; an esterified or amidated carboxyl group; hydrogen; optionally substituted aralkyl; optionally substituted cycloalkyl; and a group of formula W-(CH₂)_d, wherein d represents zero or an integer from 1 to 5 and W represents aryl having an optional substituent selected from halogen, nitro, cyano, amino, an optionally substituted carboxyl, alkylenedioxy wherein the alkylene is C₁ to C₆, and a group of formula -X-R', wherein X represents a chemical bond or a spacer group and R' represents an optionally substituted cycloalkyl or an optionally substituted heterocyclic group. Alternative embodiments, having different R₃ definitions are presented below.

Preferably, R₄ represents a group of the formula:-



25

wherein:-

R6 is selected from hydrogen; halogen; and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom; and

R7 is selected from hydrogen; halogen; nitro; cyano; and a hydrocarbon residue optionally substituted by a group bonded through an oxygen atom, a nitrogen atom or a sulphur atom.

5

In an alternative preferred embodiment, R3 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; C1 to C3 perfluoroalkyl; CN; NO₂; halogen; or R₁₁O(CH₂)_e-;

wherein R₁₁ represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R₁₂, R₁₃ and R₁₄, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R₁₂, R₁₃ and R₁₄;

For R₁₂, R₁₃ and R₁₄, either:-

(a) R₁₂, R₁₃ and R₁₄ independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; (CH₂)_fS(O)_gR₁₅; or halogen; or

(b) R₁₂ meets the definition in (a) and R₁₃ and R₁₄ together represent a 3C to 7C carbocyclic ring or a heterocyclic ring comprising from 1 to 3 heteroatoms selected from O, N and S;

R₁₅ represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

e and f independently represent 0, 1, 2, 3, 4 or 5; and
g represents 0, 1 or 2.

In this alternative embodiment, for definitions of preferred R3 substituents, reference is
5 made to WO 98/55119 or WO 99/41251, where the definition of R6 corresponds with R3
in this alternative embodiment of the present invention. These disclosures of WO
98/55119 and WO 99/41251, which provide disclosure of preferred R3 substituents, are
explicitly incorporated herein by reference.

10 In this alternative embodiment, preferably ring A has a further substituent selected from
halogen and $-Q(R16)R17$, wherein:-

Q represents N; O; S(O)_h; C(O); (CR₁₈R₁₉)_i; a single bond to R₁₆; optionally substituted
C₂ to C₆ alkenyl; or optionally substituted C₂ to C₆ alkynyl; with the proviso that when Q
is O; S(O)_h; C(O); (CR₁₈R₁₉)_i; or a single bond, R₁₇ is absent; and

15 For R₁₆ and R₁₇, either:-

(c) R₁₆ represents hydrogen or optionally substituted C₁ to C₆ alkyl; and

R₁₇ represents hydrogen; C(O)NR₁₈R₁₉; C(O)R₂₀; NR₁₈R₁₉; C(O)R₁₈;
NR₁₉C(O)R₁₈; NR₁₉C(O)NR₁₈R₁₉; NR₁₉S(O)₂R₁₈; NR₁₉S(O)₂NR₁₈R₁₉;

20 OC(O)R₁₈; OC(O)NR₁₈R₁₉; OR₁₈; S(O)_jR₁₈; S(O)_jNR₁₈R₁₉; a mono- or bi-cyclic
heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being
optionally substituted by R₂₁, R₂₂ and R₂₃, or being optionally substituted by an
optionally substituted C₁ to C₆ alkyl; or

(d) the structure $-Q(R16)R17$ represents a heterocyclic ring comprising one or more

25 heteroatoms selected from O, N and S and optionally substituted by R₂₁, R₂₂ and R₂₃; or

(e) the structure $-Q(R16)R17$ represents a 3-7 membered carbocyclic ring or =O;

For R₁₈ and R₁₉, either:-

(f) Each R₁₈ and R₁₉ independently represents a bond; hydrogen; optionally substituted

30 C₁ to C₆ alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally

substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21, R22 and R23, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R21, R22 and R23; or

5 (g) R18 and R19 together form part of an optionally substituted 3 to 9-membered ring;

R20 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; or optionally substituted aralkyl;

10

For R21, R22 and R23, either:-

(h) Each R21, R22 and R23 independently represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl;

15 R₁₈O(CH₂)_k, where R₁₈ meets the definition in section (f); (CH₂)_kS(O)_lR₂₄; or halogen; or

(i) R₂₁ is as defined in section (h) and R₂₂ and R₂₃ together represent a C3 to C7 carbocyclic ring or a heterocyclic ring containing from 1 to 3 heteroatoms selected from O, N and S;

20

R₂₄ represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

i and k independently represent 0, 1, 2, 3, 4 or 5; and

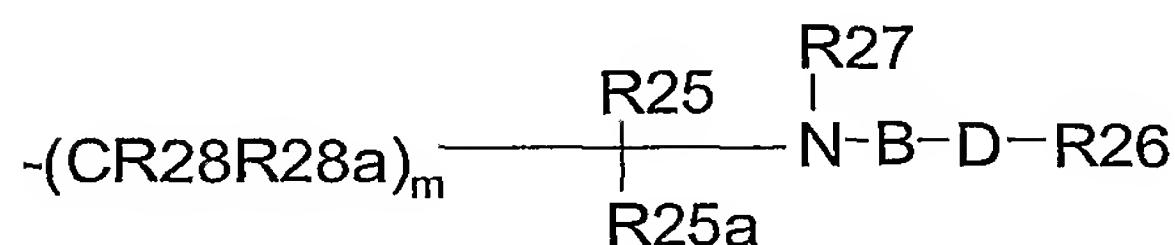
25 each h, j and l independently represent 0, 1 or 2.

In this embodiment, for definitions of a preferred further substituent of ring A, reference is made to WO 98/55119, WO 98/55123 or WO 99/41251, where the definition of -XR₇(R₈) corresponds with the further substituent of ring A in this alternative embodiment of the present invention. This disclosures of WO 98/55119, WO 98/55123 and WO 99/41251,

which provide disclosure of such a preferred further substituent, are explicitly incorporated herein by reference.

In an alternative embodiment, R1 represents the group

5



wherein:-

B represents R₂₉-Y-R₂₉, wherein Y represents optionally substituted aryl;

10

D is selected from a bond; -OR₂₉-; -C(=O)R₂₉-; -S(O)_nR₂₉-; -NR₂₉R₃₀-; -OC(=O)R₂₉-; -C(=O)OR₂₉-; -NR₃₁C(=O)R₂₉-; -C(=O)NR₃₁R₂₉-; -OS(O)_nR₂₉-; -S(O)_nOR₂₉-; and -NR₃₁S(O)_nR₂₉-;

15

For R₂₅, R_{25a}, R₂₇, R₂₈ and R_{28a} either:-

(i) R₂₅, R_{25a}, R₂₇, R₂₈ and R_{28a} are independently selected from hydrogen; optionally substituted C₁ to C₆ alkyl; optionally substituted aryl; and optionally substituted aralkyl;

20

(j) R₂₅ and R_{25a} together represent a 3-7 membered carbocyclic ring or =O; and R₂₇, R₂₈ and R_{28a} meet the definition in section (i);

(k) R₂₅, R_{25a} and R₂₇ meet the definition in section (i); and R₂₈ and R_{28a} together represent a 3-7 membered carbocyclic ring or =O;

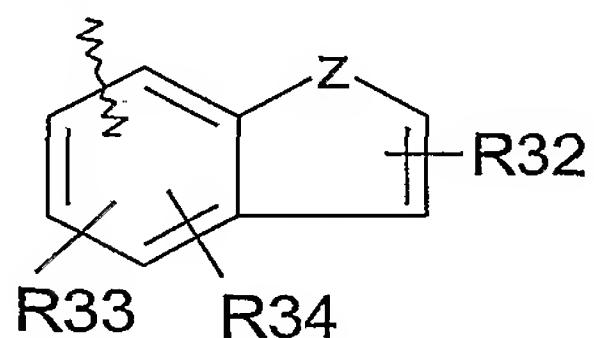
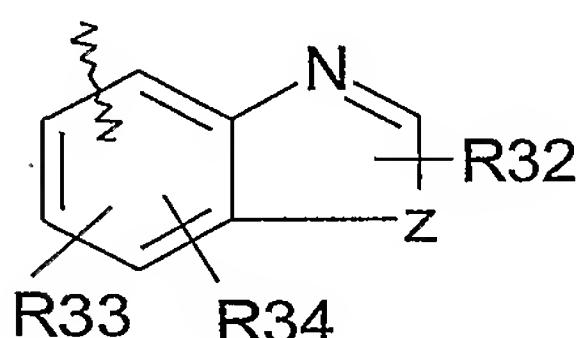
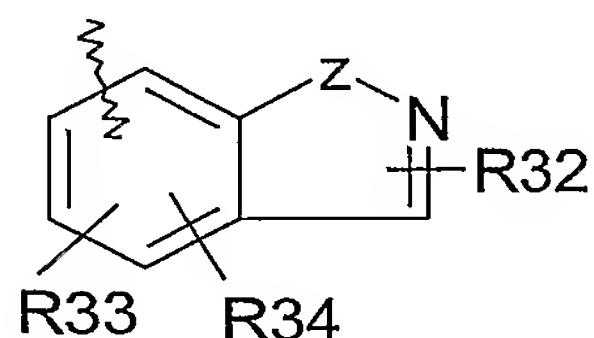
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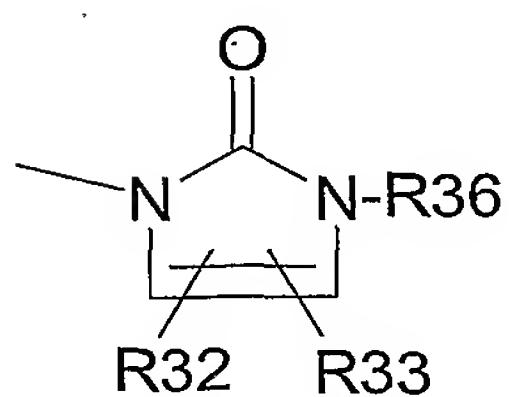
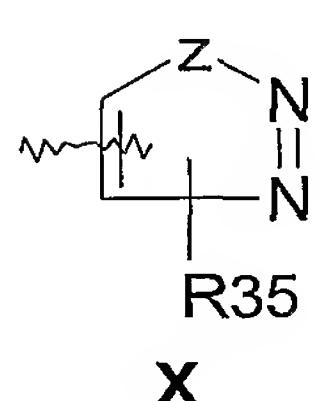
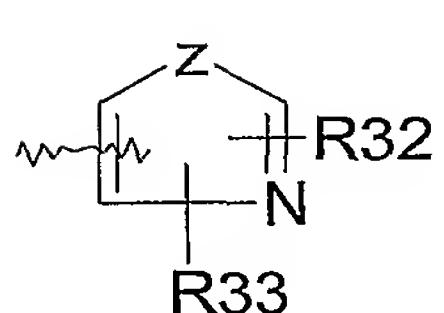
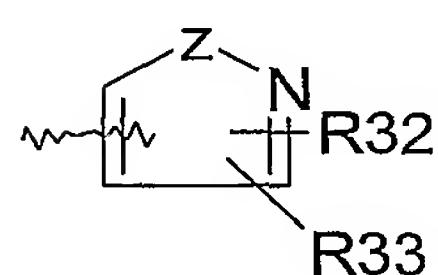
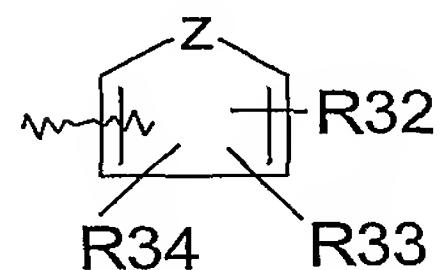
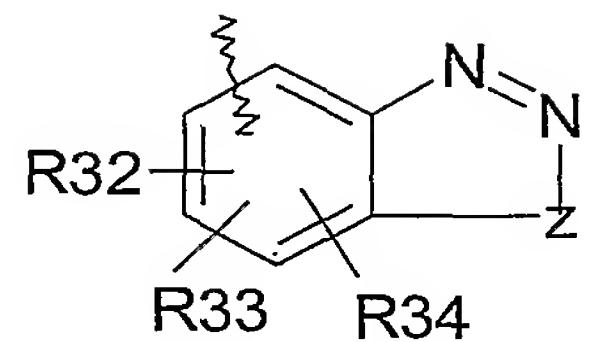
(l) R₂₅ and R₂₈ together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R_{25a}, R₂₇ and R_{28a} meet the definition in section (i);

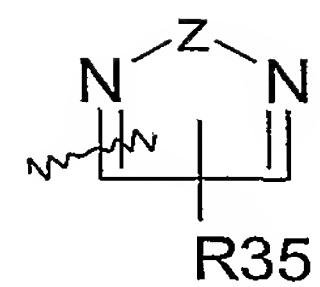
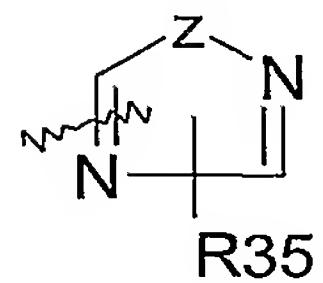
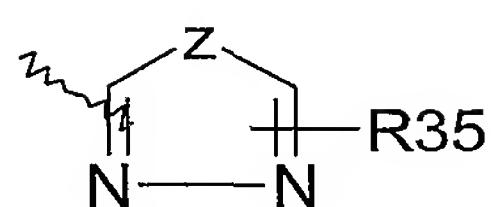
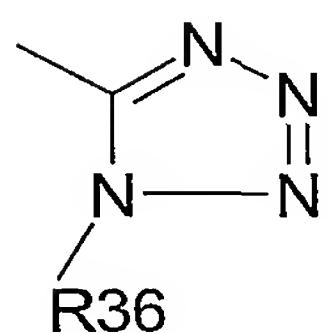
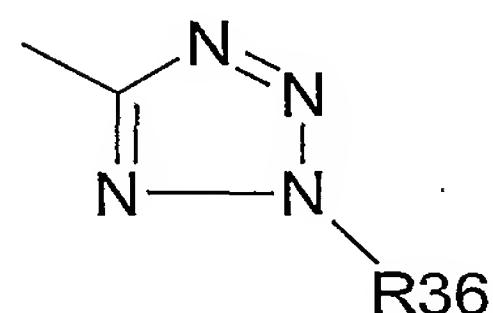
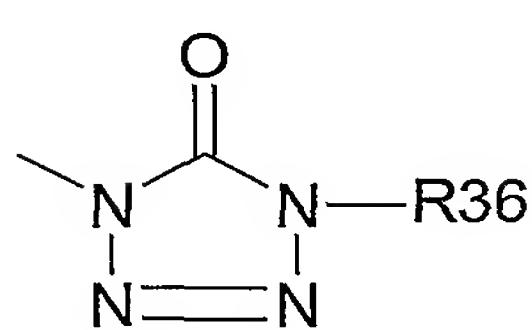
(m) R27 and R28 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25, R25a and R28a meet the definition in section (i); or

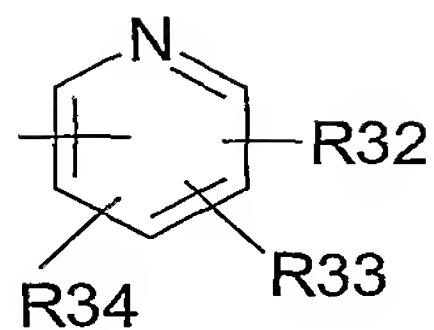
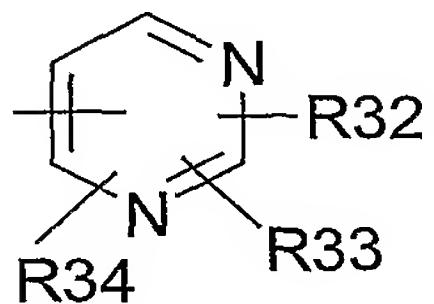
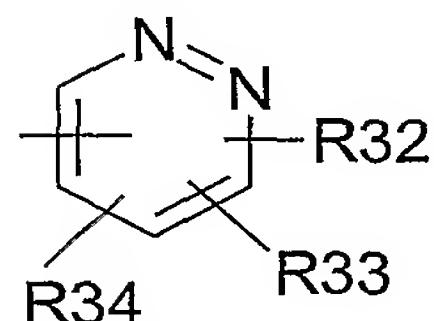
5 (n) R25 and R27 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25a, R28 and R28a meet the definition in section (i);

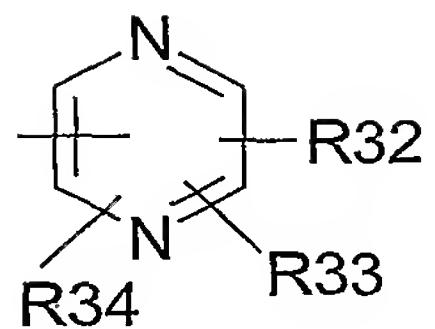
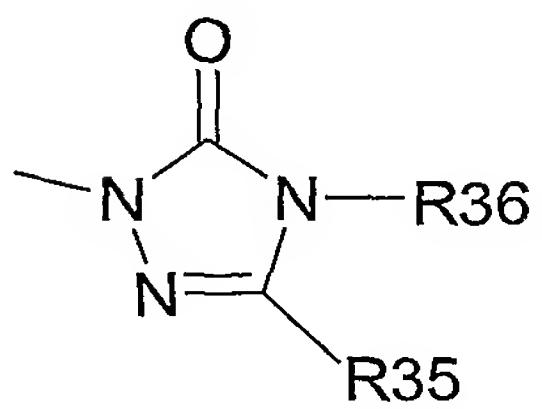
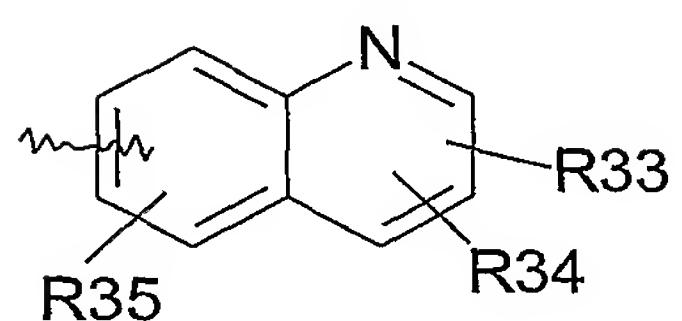
R26 represents a substituent selected from **III** to **XXIX** or an N-oxide thereof:-

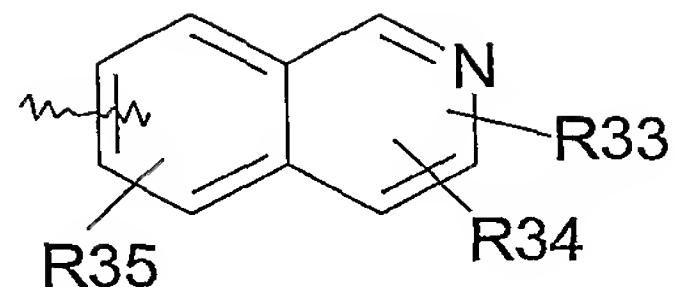
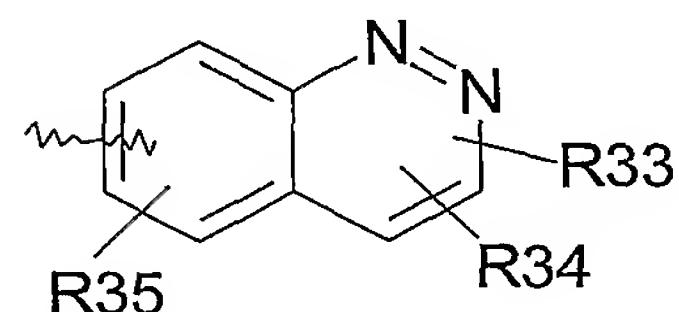
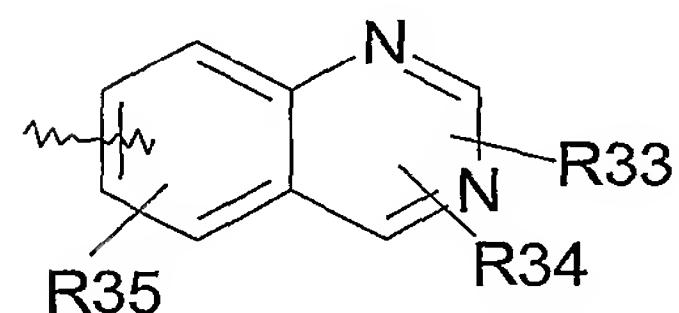
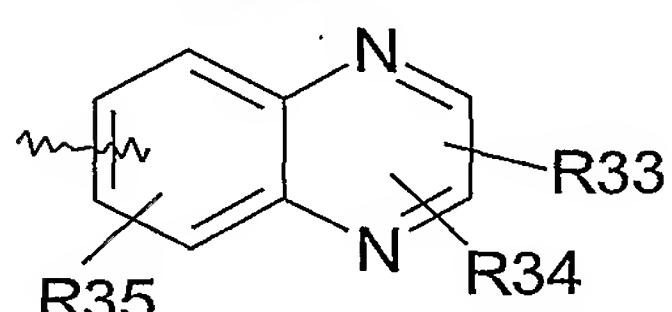
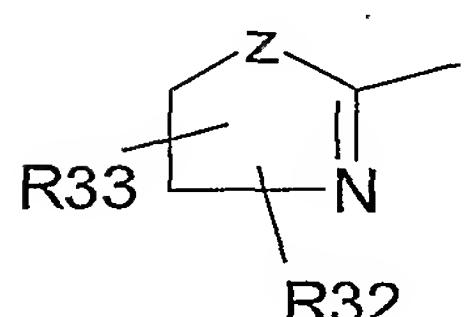
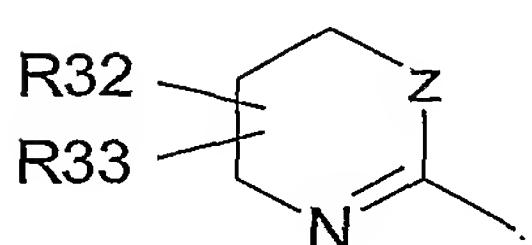
**III****IV****V**



**XII****XIII****XIV****XV****XVI****XVII**

**XVIII****XIX****XX**

**XXI****XXII****XXIII**

**XXIV****XXV****XXVI****XXVII****XXVIII****XXIX**

Each R29 is independently selected from a bond and optionally substituted C1 to C4 alkyl;

R30 represents hydrogen; optionally substituted C1 to C6 alkyl; C(O)OR37; C(O)N(R37)₂;

5 C(O)R37; or S(O)_oR37;

R31 and R36 independently represent hydrogen; optionally substituted C1 to C6 alkyl;

optionally substituted aryl; optionally substituted aralkyl; an optionally substituted

carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1

10 to 4 heteroatoms selected from O, N and S and being optionally substituted by R38, R39

and R40, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-

cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and

which ring is optionally substituted by R38, R39 and R40;

15 R32 represents hydrogen; OH; NR41R42; NR37SO₂(optionally substituted C1 to C6

alkyl); NR37SO₂(optionally substituted aryl); NR37SO₂(C1 to C3 perfluoroalkyl);

SO₂NR37(optionally substituted C1 to C6 alkyl); SO₂NR37(optionally substituted aryl);

SO₂NR37(C1 to C3 perfluoroalkyl); SO₂NR37(C(O)-optionally substituted C1 to C6

alkyl); SO₂NR37(C(O)-optionally substituted aryl); S(O)_p(optionally substituted C1 to C6

20 alkyl); S(O)_p(optionally substituted aryl); C1 to C3 perfluoroalkyl; C1 to C3

perfluoroalkoxy; optionally substituted C1 to C6 alkoxy; COOH; halogen; NO₂; or CN;

R33 and R34 are independently selected from hydrogen; optionally substituted C1 to C6

alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to

25 C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl;

R37O(CH₂)_q-; R37C(O)O(CH₂)_q-; R37OC(O)(CH₂)_q-; -(CH₂)_qS(O)_rR', where R' is

hydrogen, optionally substituted C1 to C6 alkyl, C1 to C3 perfluoroalkyl or optionally

substituted aryl; -(CH₂)_qC(O)N(R37)₂; or halogen;

30 R35 meets a definition of either R32 or R33;

Each R37 independently represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; or an optionally substituted 3 to 7-membered carbocyclic ring;

5

R38, R39 and R40 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $(CH_2)_sS(O)_tR43$; or halogen;

10

For R41 and R42, either:-

(o) R41 represents hydrogen or optionally substituted C1 to C6 alkyl; and

R42 represents hydrogen; C(O)NR18'R19'; C(O)R20'; NR18'R19'; C(O)R18'; NR19'C(O)R18'; NR19'C(O)NR18'R19'; NR19'S(O)₂R18'; NR19'S(O)₂NR18'R19'; OC(O)R18'; OC(O)NR18'R19'; OR18'; S(O)_uR18'; S(O)_uNR18'R19'; a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21', R22' and R23', or being optionally substituted by an optionally substituted C1 to C6 alkyl; wherein R18', R19', R20', R21', R22' and R23' meet a definition respectively of R18, R19, R20, R21, R22 and R23 in claim 7; or

(p) the structure -N(R41)R42 represents a heterocyclic ring comprising one or more heteroatoms selected from O, N and S and optionally substituted by R21', R22' and R23'; wherein R21', R22' and R23' meet a definition respectively of R21, R22 and R23 in claim 7;

25

R43 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

Z represents O, S or NR18';

30

R18' meets a definition of R18 in section (f) of claim 7;

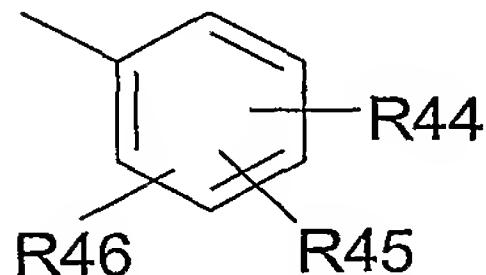
Each m, q and s independently represent 0, 1, 2, 3, 4 or 5; and
 n, o, p, r, t and u independently represent 0, 1 or 2.

5

In this alternative embodiment, for definitions of preferred R1 substituents, reference is made to WO 98/55119, WO 99/51231 or WO 99/41251, where the definition of –(CR₉R_{9a})_m-CR₁₀(R_{10a})(NR₂((A)-(B)-R₁) or the definition of –(CR₉R_{9a})_m-CR₁₀(R_{10a})(NR₂((A)-R₁) corresponds with R1 in this alternative embodiment of the present invention. These disclosures of WO 98/55119, WO 99/51231 and WO 99/41251, which provide disclosure of preferred R1 substituents, are explicitly incorporated herein by reference.

In an alternative embodiment, R2 represents represents a substituent of formula XXX:-

15



XXX

R44, R45 and R46 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; (CH₂)_vS(O)_wR47; or halogen;

R47 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

25

v represents 0, 1, 2, 3, 4 or 5; and

w represents 0, 1 or 2.

In this alternative embodiment, for definitions of preferred R2 substituents, reference is made to WO 98/55119, where the definition of the phenyl substituted by R3 to R5 in WO 5 98/55119 corresponds with R2 in this alternative embodiment of the present invention.

This disclosure of WO 98/55119, which provides disclosure of preferred R2 substituents, is explicitly incorporated herein by reference.

In an alternative embodiment, R1 meets the definition of $-X-(A)-CR_9(R_{9a})-(B)-NR_{10}(R_{11})$ disclosed in WO 97/44037, WO 99/41251 or WO 97/44339, and these disclosures are explicitly incorporated herein by reference.

In an alternative embodiment, R2 meets the definition of Y disclosed in WO 97/44037 or the definition of the phenyl substituted by R₂, R₃ and R₄ given in the formula I disclosed 15 in WO 97/44339 or WO 99/41251, and these disclosures are explicitly incorporated herein by reference.

In an alternative embodiment, R3 meets a definition of R₅, R₆, R₇ or R₈ disclosed in WO 97/44037 or WO 97/44339, and ring A optionally has at least one further substituent 20 meeting the definition of R₅, R₆, R₇ or R₈ disclosed in WO 97/44037 or WO 97/44339.

The disclosure in WO 97/44037 and WO 97/44339 relating to R₅, R₆, R₇ or R₈ is explicitly incorporated herein by reference.

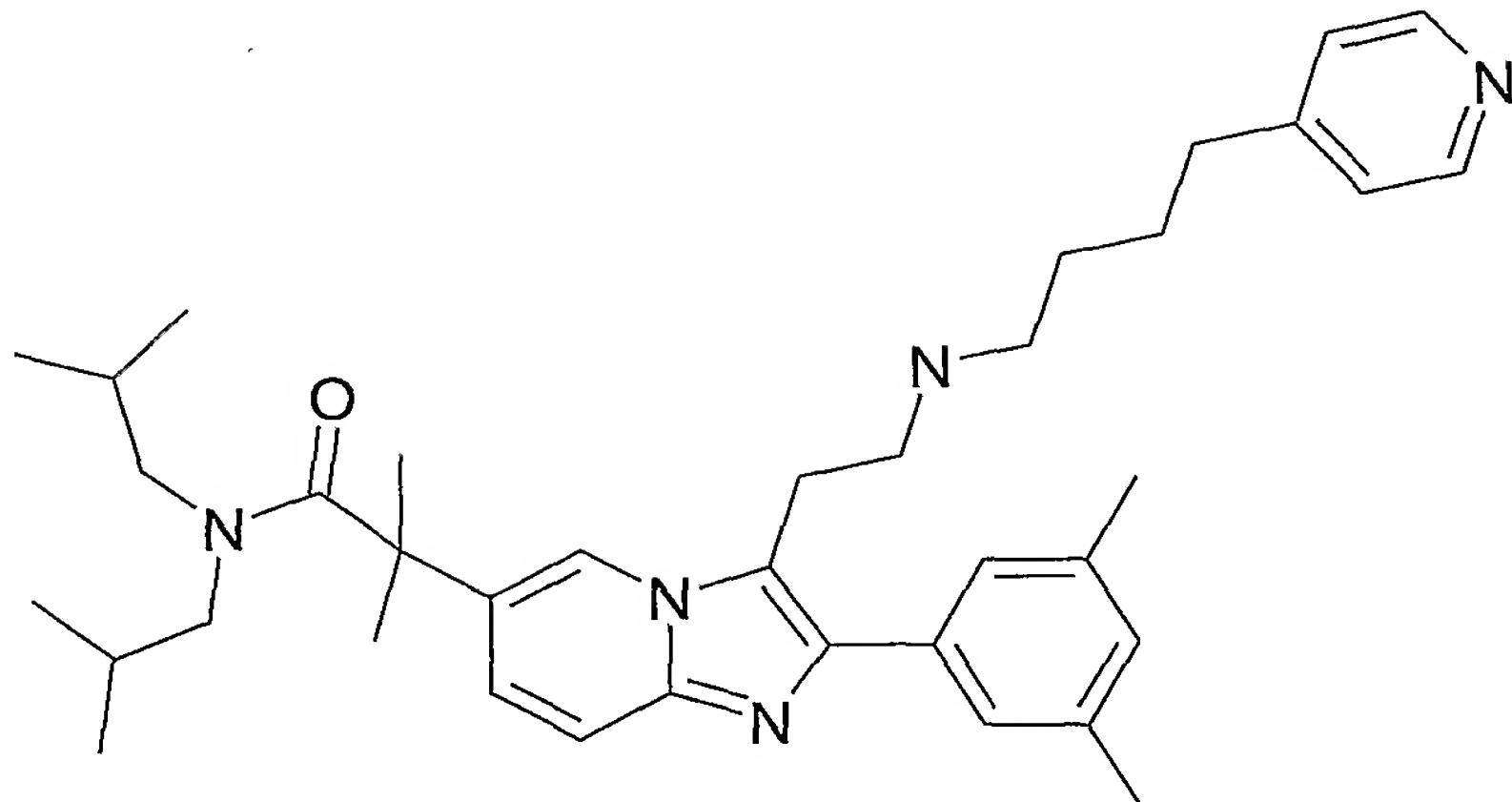
In the present specification, unless otherwise indicated, an alkyl, alkylene or alkenyl 25 moiety (eg, the alkyl moiety of an alkylaryl substituent) may be linear or branched. Where C1 to C6 alkyl is mentioned, preferably this is C2 to C4 alkyl, and more preferably methyl. Where C2 to C6 alkenyl is mentioned, preferably this is C2 to C4 alkenyl, most preferably C2 or C3 alkenyl.

30 The term "alkylene" refers to $-CH_2-$. Thus, C8 alkylene for example is $-(CH_2)_8-$.

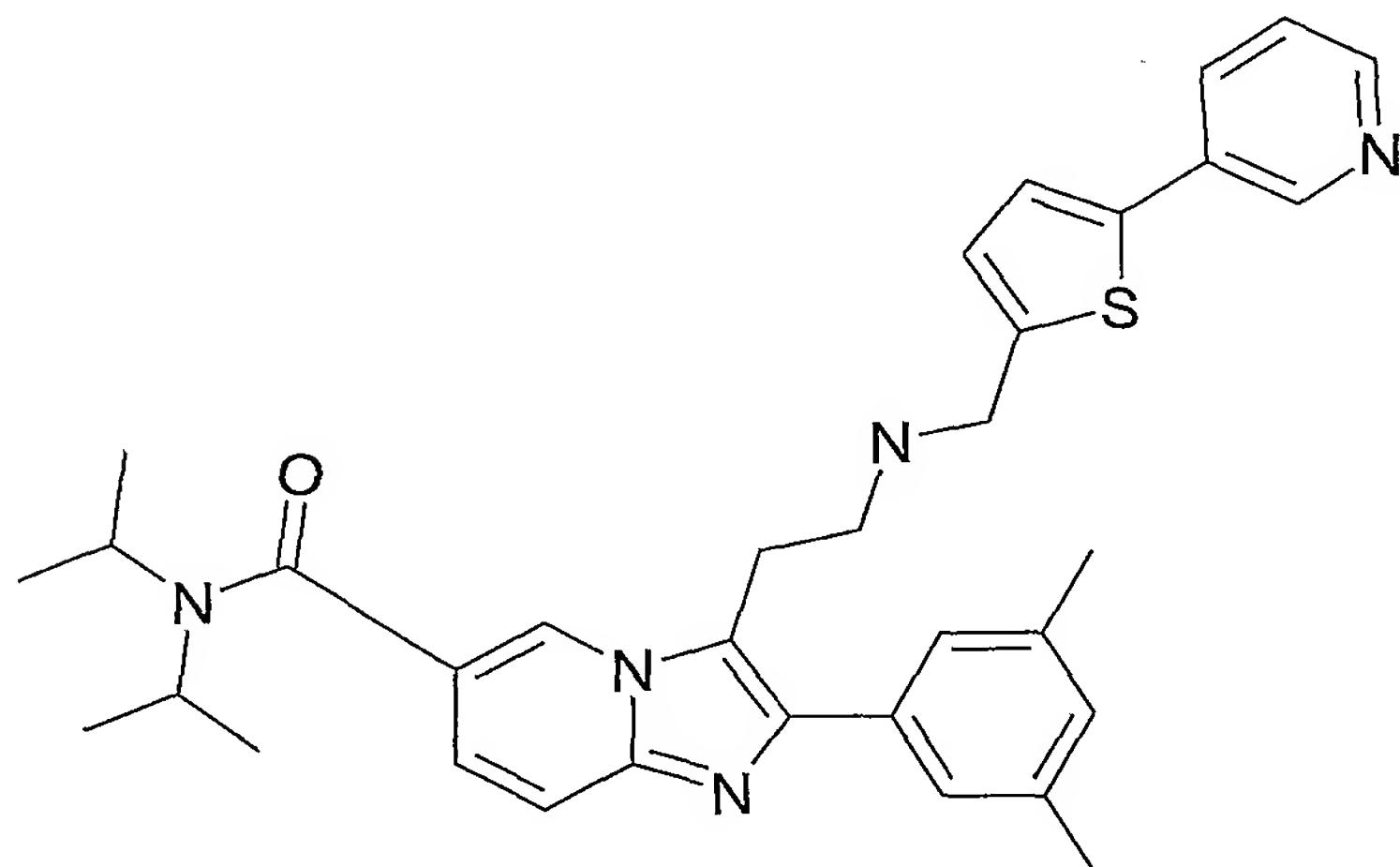
Where optional substitution is mentioned at various places above, this refers to one, two, three or more optional substituents. Unless otherwise indicated above (ie, where a list of optional substituents is provided), each substituent can be independently selected from C1 to C8 alkyl (preferably C2 to C6 alkyl, and most preferably methyl); O(C3 to C8 cycloalkyl), preferably O-cyclopropyl, or O-cyclobutyl or O-cyclopentyl; O(C1 to C6 alkyl), preferably Omethyl or O(C2 to C4 alkyl); halo, preferably Cl or F; CHal₃, CHHal₂, CH₂Hal, OCHal₃, OCHHal₂ or OCH₂Hal, wherein Hal represents halogen (preferably F); CH₂OR, NRCOR', NRSO₂R' or N-R-R', wherein R and R' independently represent H or C1 to C8 alkyl (preferably methyl or C2 to C6 alkyl or C2 to C4 alkyl) , or N-R-R' represents an optionally substituted C3 to C8, preferably C3 to C6, heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; H; or COOR'' or COR'', R'' representing H, optionally substituted phenyl or C1 to C6 alkyl (preferably methyl, ethyl, *i*-propyl or *t*-butyl). For optional substitution of the heterocyclic ring represented by N-R-R', at least one (eg, one, two or three) substituents may be provided independently selected from C1 to C6 alkyl (preferably C2 to C4 alkyl, more preferably methyl); phenyl; OCF₃; OCHF₂; -O(C1-C8 alkyl), preferably -O-methyl, -O-ethyl or -O(C3 to C6 alkyl); -C(O)O(C1-C8 alkyl), preferably -C(O)O-methyl, -C(O)O-ethyl, -C(O)O-*tert*-butyl or -C(O)O(C3 to C6 alkyl); -C(O)O-phenyl; -O-phenyl; -C(O) (C1-C8 alkyl), preferably -C(O)-methyl, -C(O)-ethyl or -C(O)(C3 to C6 alkyl) ; -C(O)OH; -S(C1-C8 alkyl), preferably -S-methyl, -S-ethyl or -S(C3 to C6 alkyl); OH; halogen (eg, F, Cl or Br), NRR' where R and R' are independently H or C1 to C6 alkyl (preferably C2 to C4 alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

25

Particularly preferred compounds according to the present invention are:-



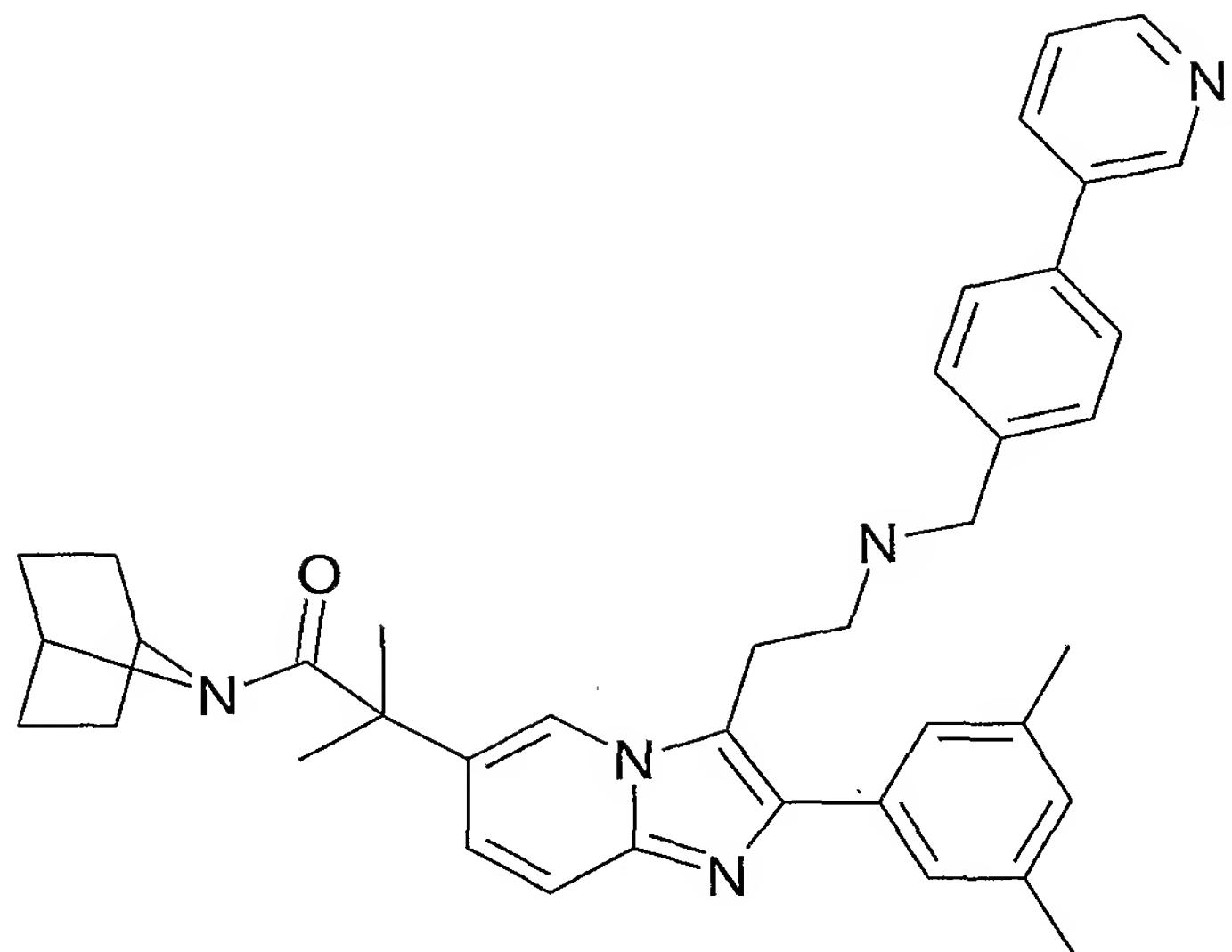
5 2-{2-(3,5-Dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-N,N-diisobutyl-isobutyramide;



10

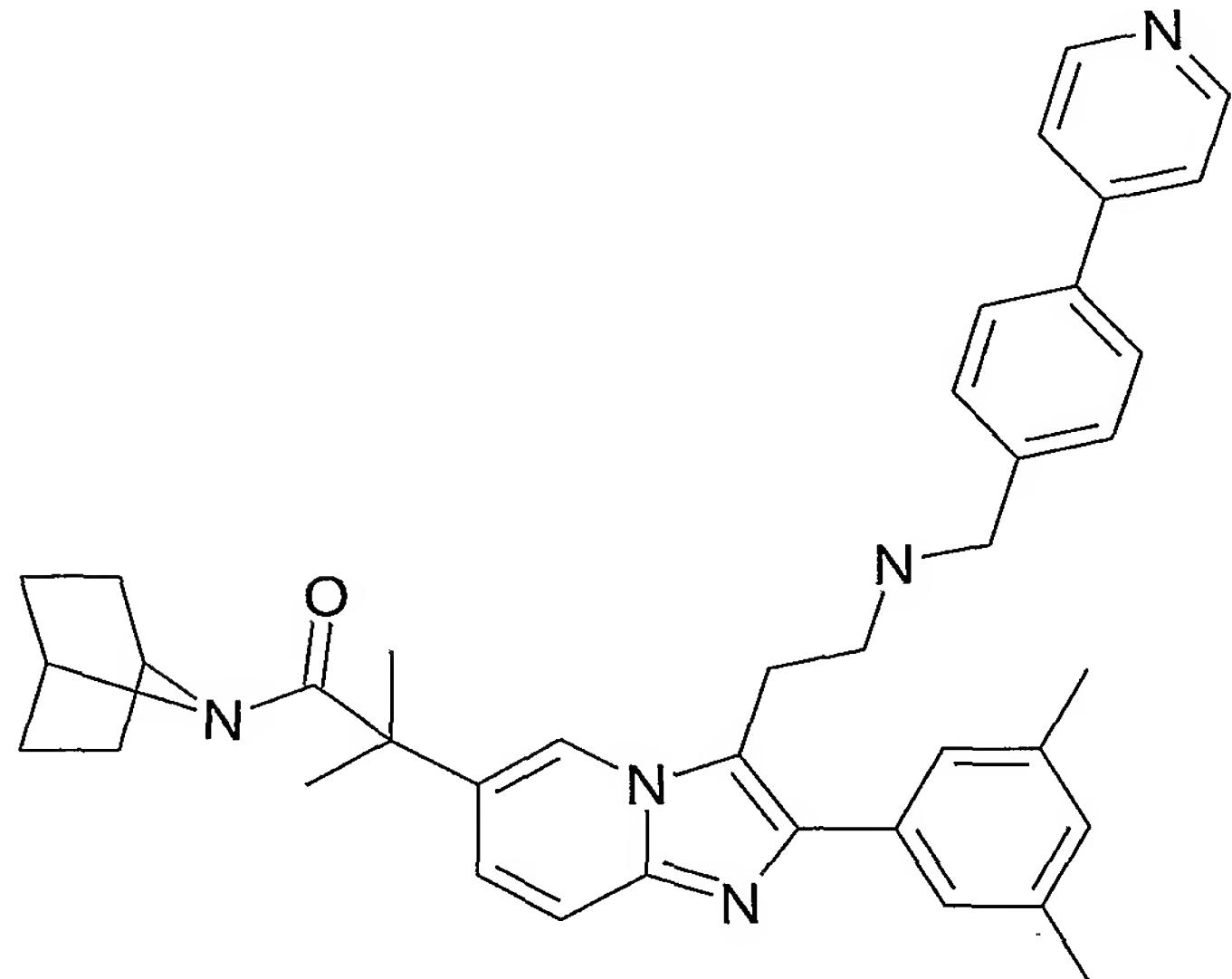
2-(3,5-Dimethyl-phenyl)-3-{2-[(5-pyridin-3-yl-thiophen-2-ylmethyl)-amino]-ethyl}-imidazo[1,2-a]pyridine-6-carboxylic acid diisopropylamide;

15



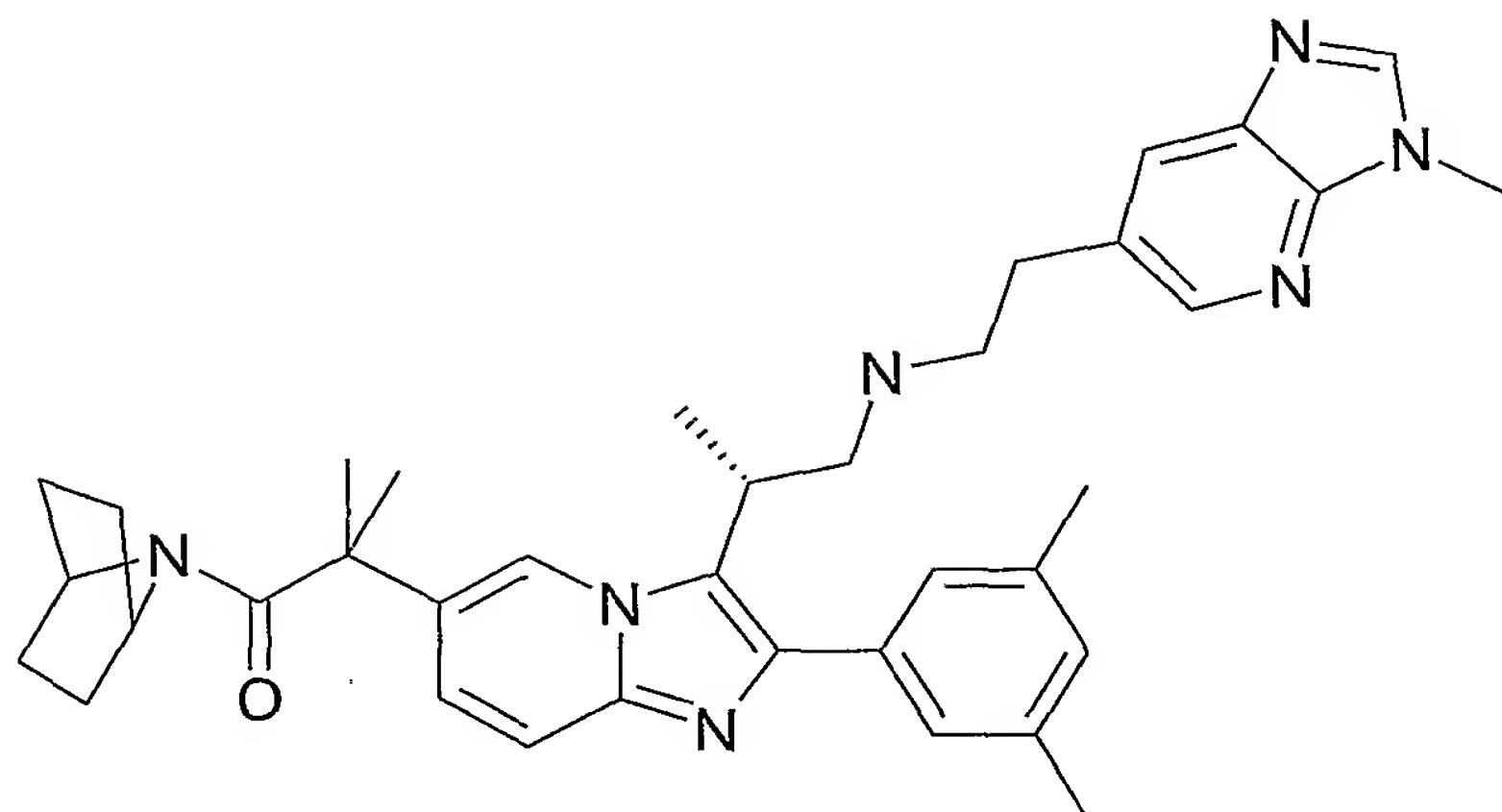
1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-3-yl-benzylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-2-methyl-propan-1-one;

5

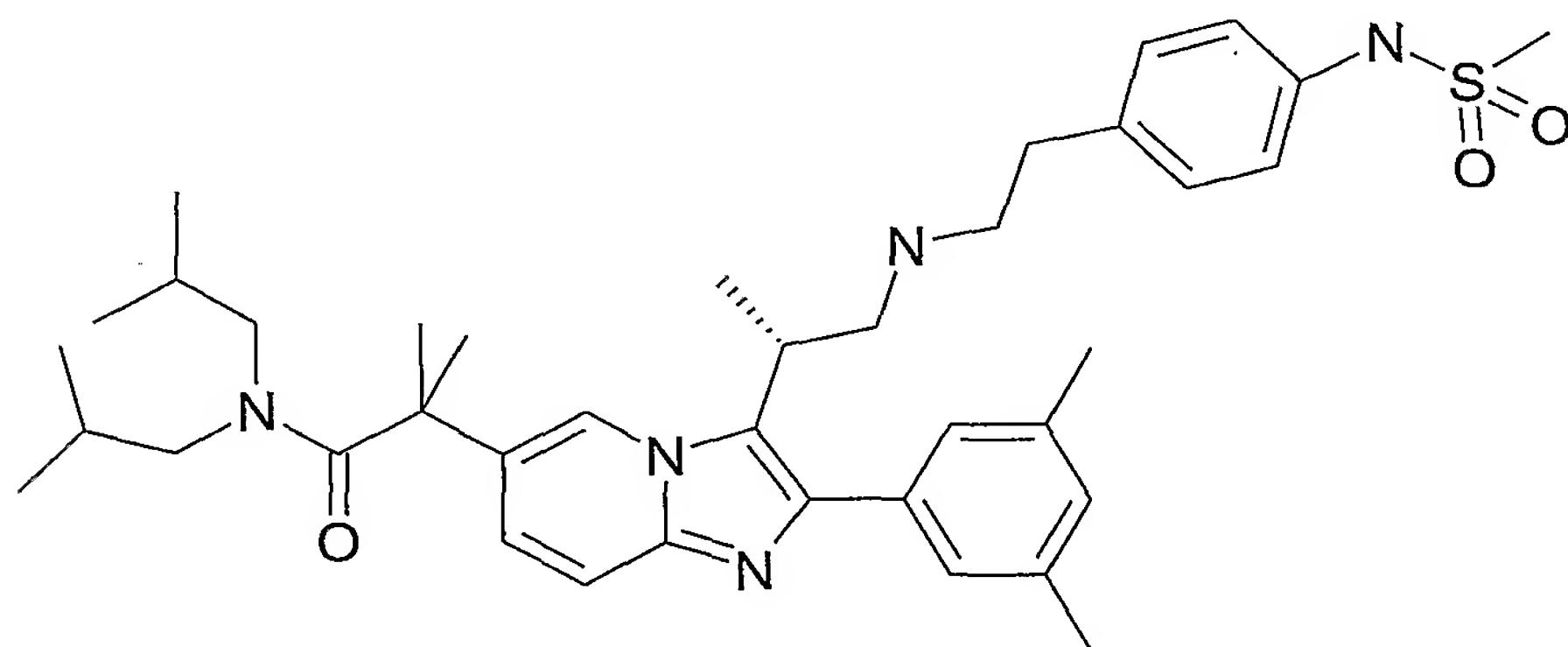


1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-benzylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-2-methyl-propan-1-one;

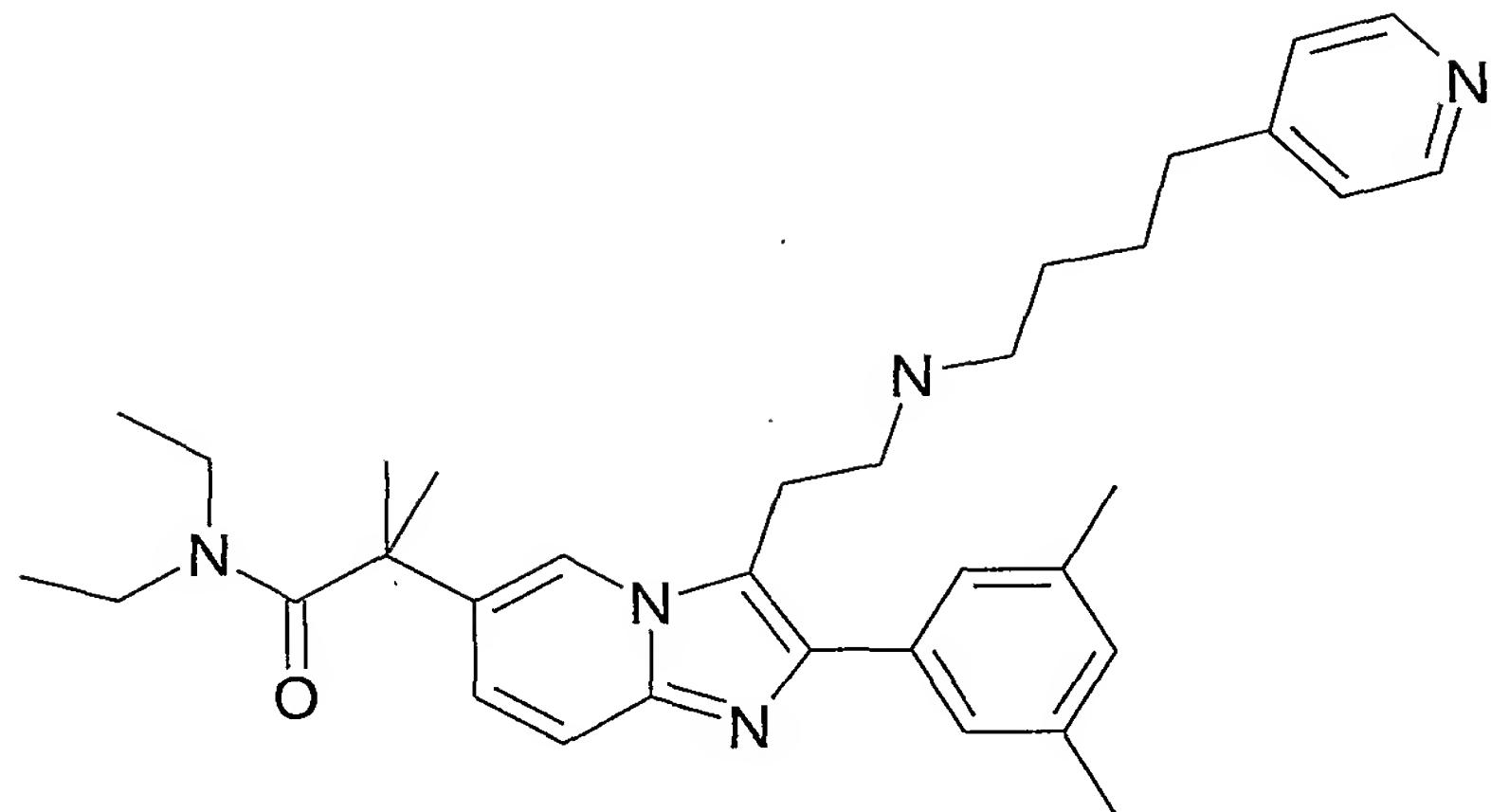
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1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-(2-(3,5-dimethyl-phenyl)-3-{(R)-1-methyl-2-[2-(3-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-ethylamino]-ethyl}-imidazo[1,2-*a*]pyridin-6-yl)-2-methyl-propan-1-one;

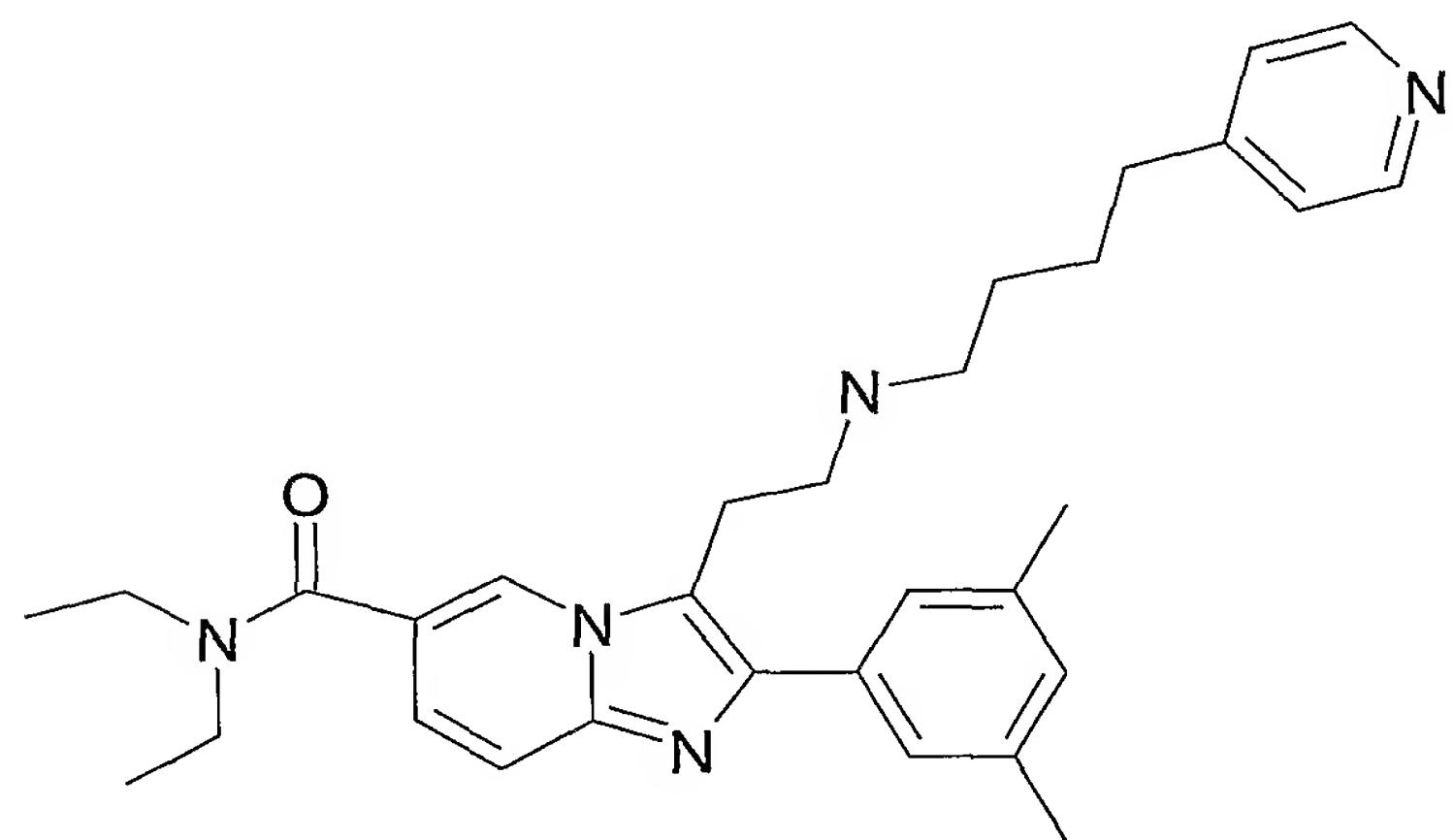


2-(2-(3,5-dimethyl-phenyl)-3-{(R)-2-[2-(4-methanesulfonylamino-phenyl)-ethylamino]-1-methyl-ethyl}-imidazo[1,2-a]pyridin-6-yl)-*N,N*-diisobutyl-isobutyramide;



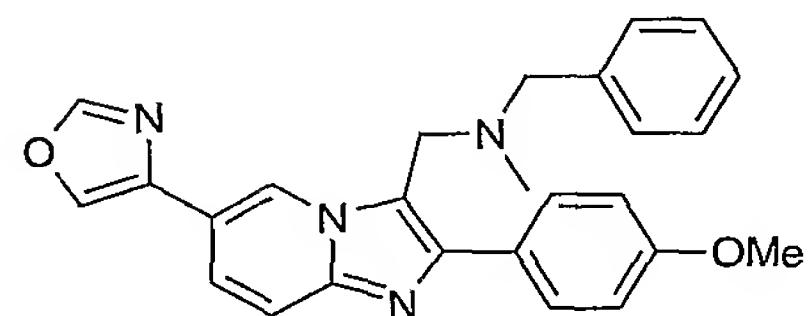
2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-*a*]pyridin-6-yl}-*N,N*-diethyl-isobutyramide;

5

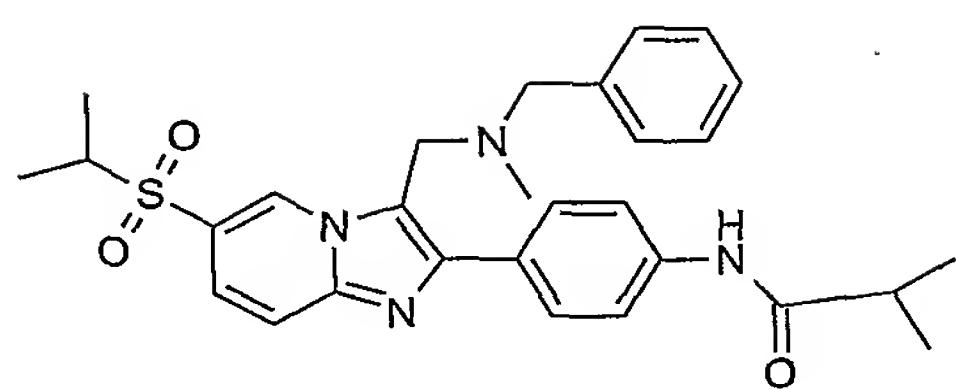


2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-*a*]pyridine-6-carboxylic acid diethylamide;

10

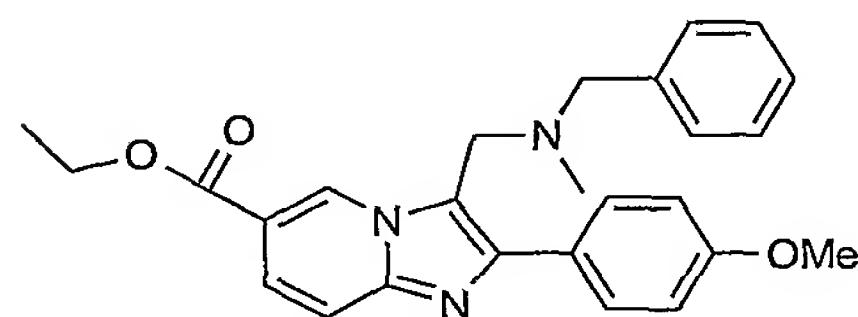


Benzyl-[2-(4-methoxyphenyl)-6-oxazol-4-yl-imidazo[1,2-*a*]pyridin-3-ylmethyl]-methylamine;

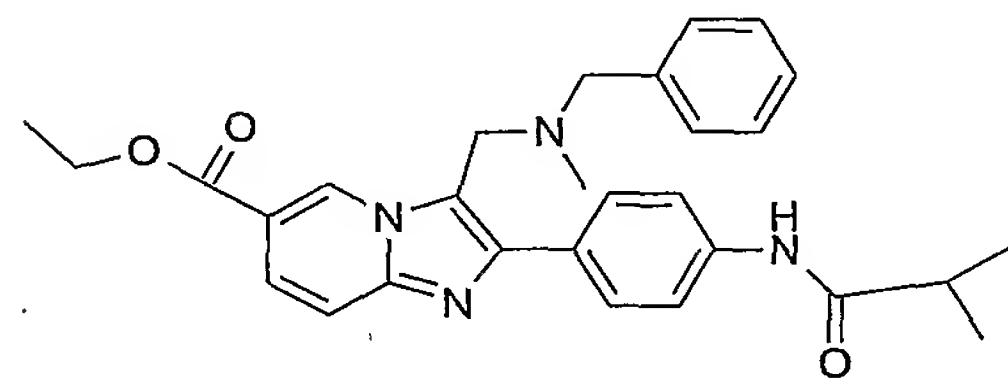


Propane-2-sulfonic acid 3-[(benzylmethylamino)-methyl]-2-[4-(2-methylpropanoylamino)-phenyl]-imidazo[1,2-a]pyridin-6-yl ester;

5

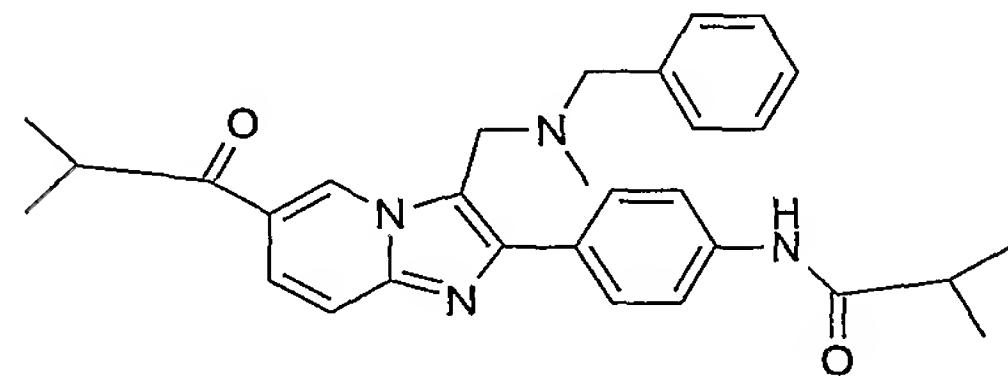


3-[(Benzylmethylamino)-methyl]-2-(4-methoxyphenyl)-imidazo[1,2-a]pyridine-6-carboxylic acid ethyl ester;



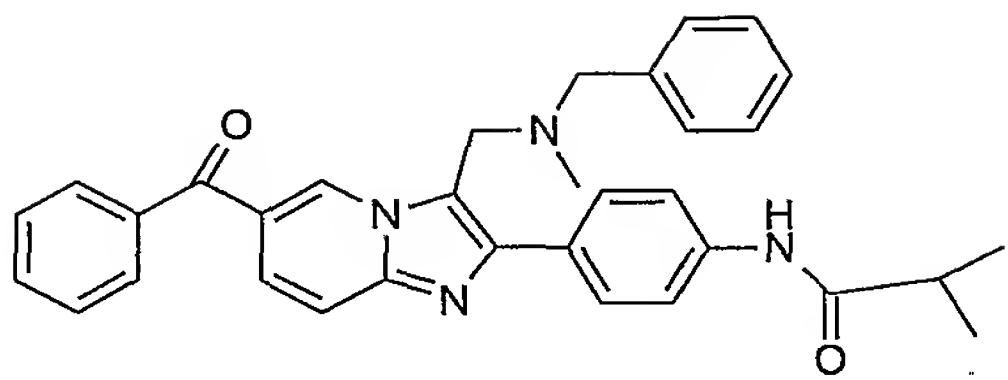
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2-(4-Acetylaminophenyl)-3-[(benzylmethylamino)-methyl]-imidazo[1,2-a]pyridine-6-carboxylic acid ethyl ester;

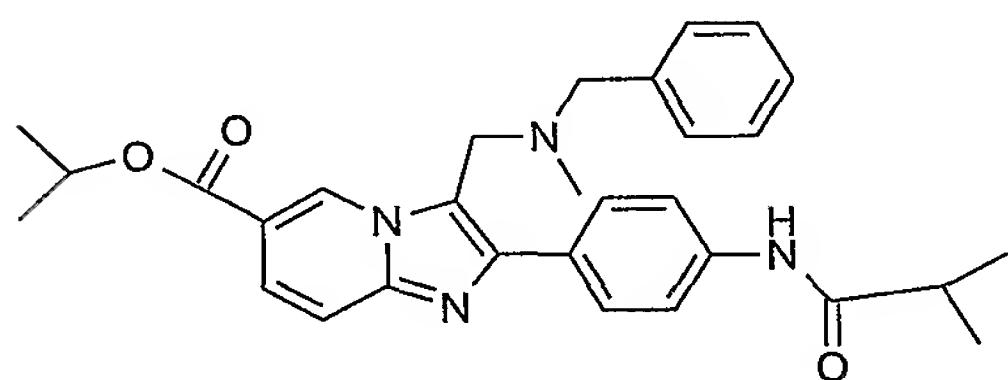


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N-{4-[3-(Benzylmethylamino)-methyl]-6-(2-methylpropanoyl)-imidazo[1,2-a]pyridin-2-yl}-phenyl-isobutyramide;

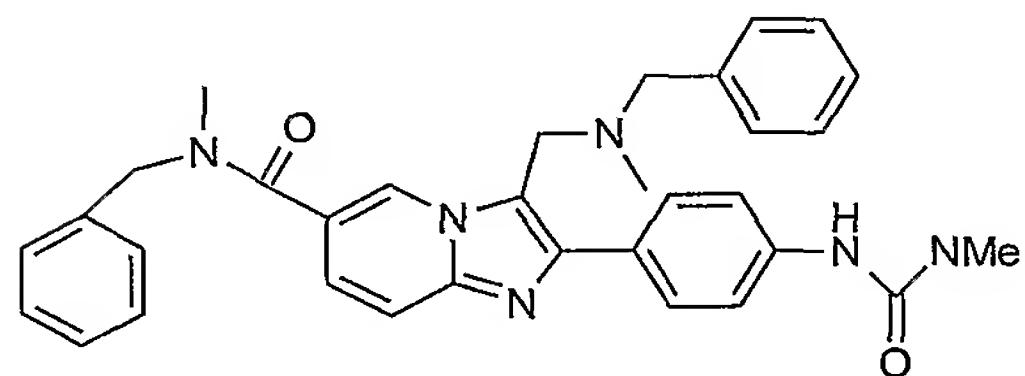


N-{4-[3-(Benzylmethylamino)-methyl]-6-(1-phenylmethanoyl)-imidazo[1,2-a]pyridin-2-yl}-phenyl-isobutyramide;



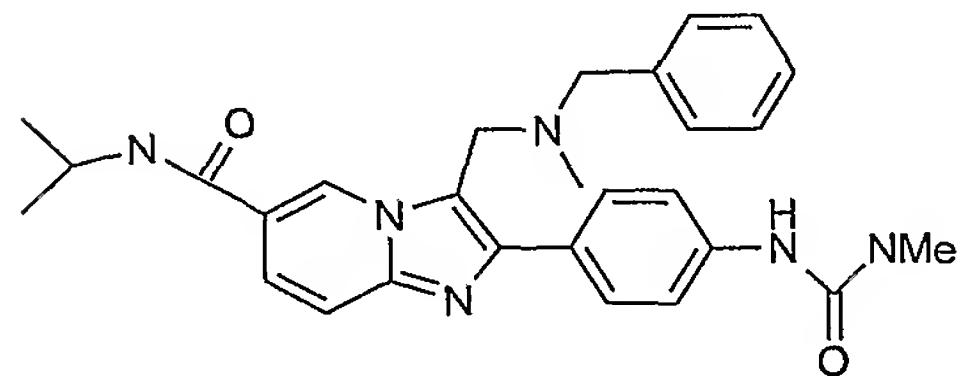
5

3-[(Benzylmethylamino)-methyl]-2-[4-(2-methyl-propanoylamino)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropyl ester;



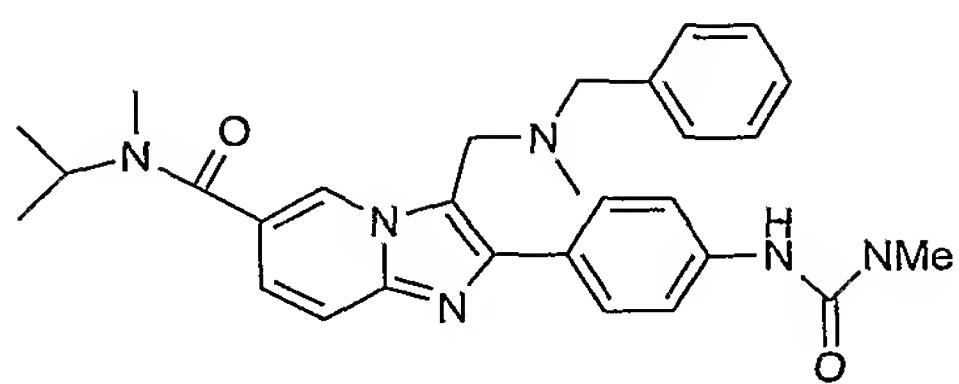
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3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid benzylmethylamide;



15

3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropylamide; and



3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropylmethylamide.

5 The invention also contemplates pharmaceutically acceptable salts and solvates of these compounds and other compounds of formula I or II. Compounds of formula I or II may be converted to pharmaceutically acceptable salts and solvates thereof, preferably acid addition salts, such as hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartarate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or alkali metal salts
10 such as sodium or potassium salts.

Full guidance is given below on processes for producing compounds according to the invention. It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the
15 starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula I or II may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in
20 Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

EXPERIMENTAL

The following reaction schemes and examples provide general guidance on how to produce compounds according to the invention. It will be apparent to the skilled addressee that the choice of reagents may need to be changed from those shown in order to produce a particular compound according to the invention, and the skilled person can make a routine choice of reagents depending on the final compound to be synthesised. Further general guidance on producing compounds according to the present invention can be found in WO 98/55119, WO 99/51231, WO 97/44041, and WO 97/14697.

10

GENERAL REACTION SCHEMES

Definitions For Schemes

In the following schemes, the following definitions apply:-

15

For R1 and R2, either:-

(i) R1 = -C(X)NR₅R₆; -C(=NCN)NR₅R₆; -C(=CHNO₂)NR₅R₆; an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing from 20 1 to 5 heteroatoms independently selected from O, N and S; optionally substituted C₁ to C₈ alkyl; optionally substituted aryl; or optionally substituted aralkyl, where the alkyl moiety is C₁ to C₈;

R2 = H; optionally substituted C₁ to C₈ alkyl; optionally substituted aryl; optionally substituted aralkyl; -R₇-R₈, wherein R₇ represents optionally substituted C₁ to 25 C₈ alkyl and R₈ represents an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing from 1 to 5 heteroatoms independently selected from O, N and S; optionally substituted C₂ to C₁₂ alkenyl; or optionally substituted alkenylaryl, wherein the alkenyl moiety is C₂ to C₁₂; and

A = a single bond; optionally substituted C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or $-R-Ar-R'$, where R and R' are independently selected from a bond, optionally substituted C1 to C8 alkylene and a C2 to C12 group having at least one alkene double bond; and Ar represents optionally substituted aryl; or

5 (ii) the structure N-R1R2 represents a 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S and optionally fused to a C5 to C10 ring structure, N-R1R2 being optionally substituted;

10 For R3 and R4, either R3 is selected from (iii) and R4 selected from (iv); or R3 is selected from (iv) and R4 selected from (iii):-

15 (iii) H; -ZR9, halogen; -ZC(O)NR9R10; -ZC(O)OR9; -ZC(O)SR9; -ZC(O)R9; C(R9)=N-OR10; -ZNR9C(O)NR10R11; -ZNR9SO₂R10; -ZSO₂R9R10; -ZCR9(CN)₂; -ZN(R9)CN; or an optionally substituted 3- to 6-membered heterocyclic ring containing from 1 to 3 heteroatoms independently selected from O, N and S;

20 (iv) -Z'M, wherein

M represents a mono- or bi-cyclic aromatic ring structure optionally having at least one substituent selected from CN; NR12R13; an optionally substituted C1 to C8 alkyl; optionally substituted C1 to C8 alkoxy; halogen; (CH₂)_b-C(O)NR12R13; NR12-C(O)NR13R14; (CH₂)_b-SO₂NR12R13; NR12C(O)R13; NR12SO₂R13; (CH₂)_bOH; NR12CN; and CR12(CN)₂;

25 Wherein each R5, R6, R10, R11, R12, R13 and R14 is independently selected from H; optionally substituted C1 to C8 alkyl and optionally substituted aryl;

30 R9 is selected from H; optionally substituted C1 to C8 alkyl; optionally substituted aryl;

-R-Ar, where R represents C1 to C8 alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

5

X = O; S; or NR^{'''}, where R^{'''} is H or C1 to C8 alkyl;

Y = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or a C2 to C12 group having at least one alkyne triple bond;

Z = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen, C1 to C8 alkyl, CH₂F, CHF₂, and C3 to C8 cycloalkyl;

10

Z' = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen, C1 to C8 alkyl, CH₂F, CHF₂, and C3 to C8 cycloalkyl;

15

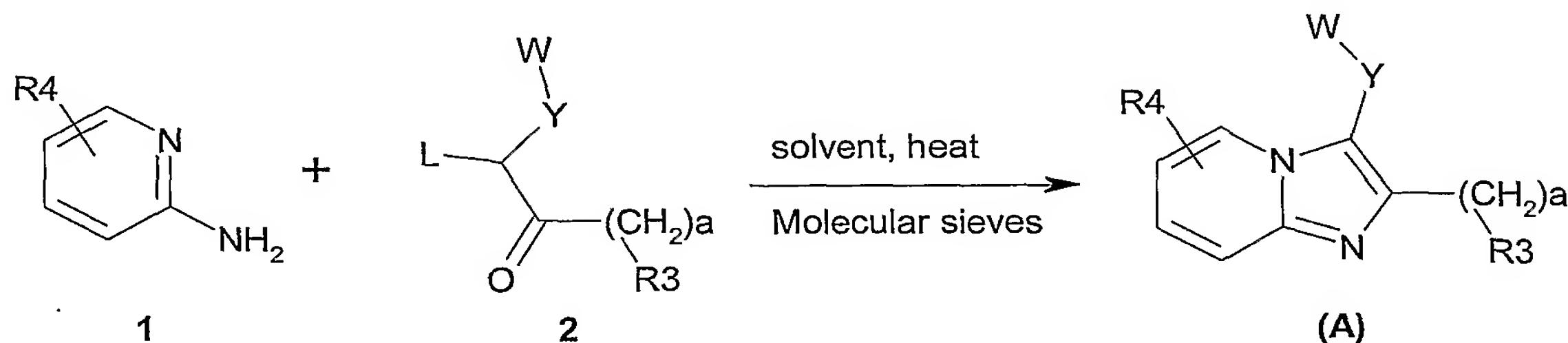
a = zero or an integer from 1 to 8;

each b independently represents zero or an integer from 1 to 8;

20

Wherein ring **B** is optionally further substituted.

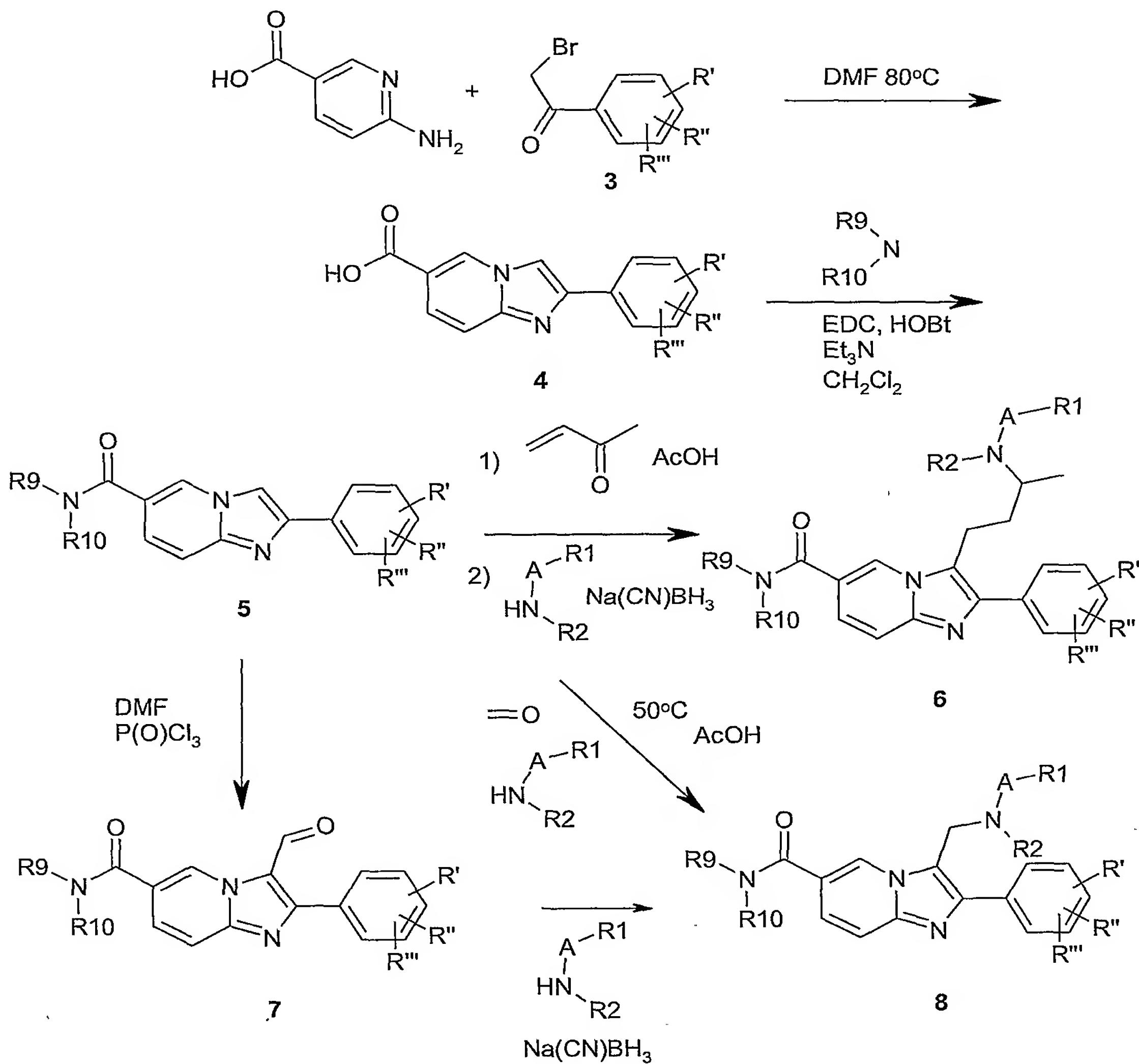
Schemes



Scheme a

L=leaving group e.g. Cl, Br, I, OMeSyl, OTosyl or H, W = epoxide or aziridines
W=group for elaboration into N-(A)-R1R2.

Imidazo[1,2- α]pyridines of the structure (**A**) can be prepared by the condensation of a suitable substituted 2-aminopyridine **1** and a ketone **2** bearing a leaving group α to the carbonyl group (Br preferred group). Heating at a temperature between 25 °C and 120 °C, preferably 80 °C, in a suitable solvent such as *N,N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), toluene, xylene, *t*-BuOH, preferable DMF, with or without the molecular sieves, for a period of 1 to 24 h, effects the condensation. With appropriately substituted groups (e.g. W), the amine group -N(-(A)-R1)R2 can then be installed by standard chemistry known to those skilled in the art which is detailed below.



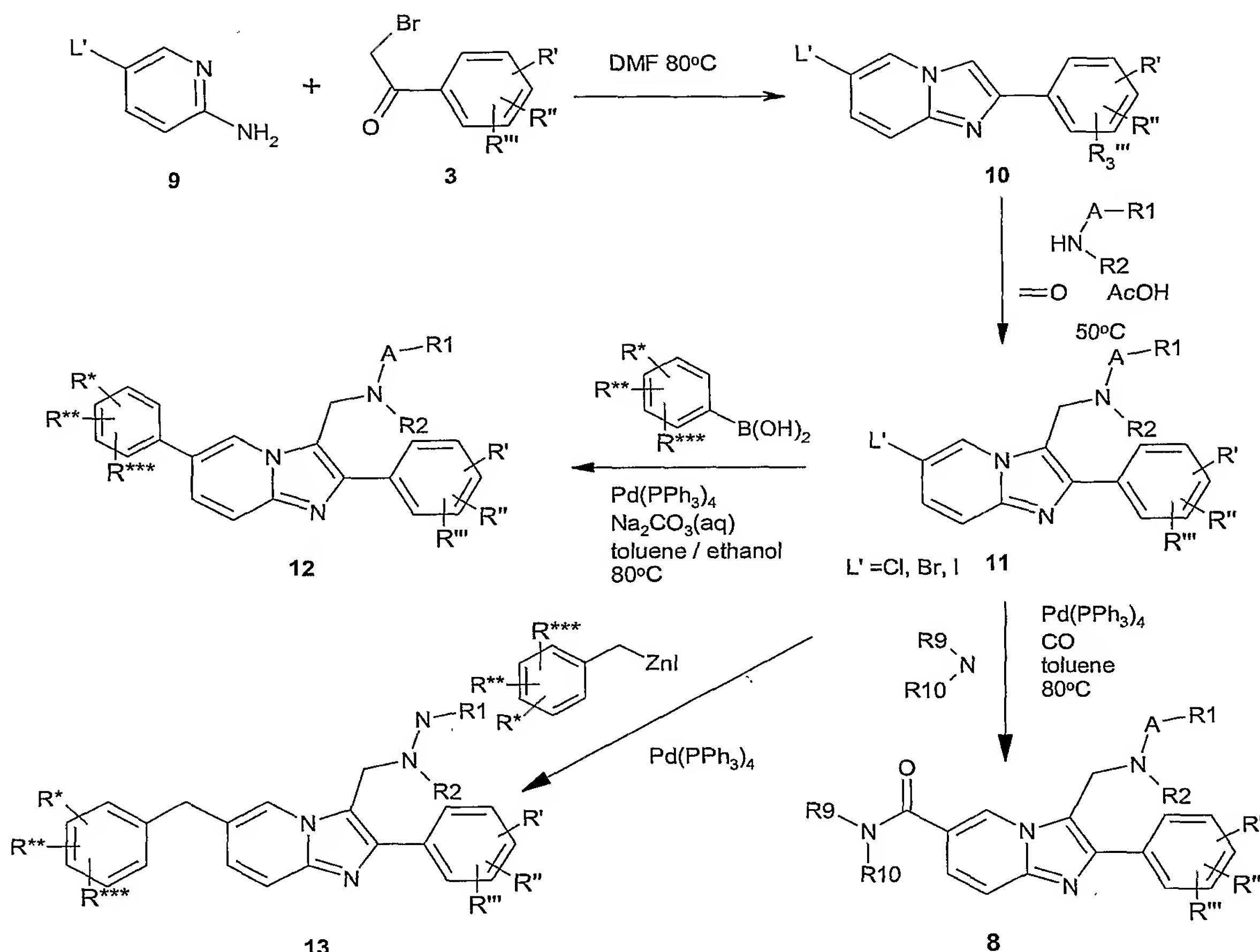
Scheme b

For example, Scheme b shows a general synthesis of 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridine commencing with commercially available 2-aminopyridine and 2'-bromoacetophenone. Thus, condensation of 6-aminonicotinic acid and a 2'-bromoacetophenone 3, under the preferred conditions noted above for the key cyclisation, yields the bicyclic 4. Condensation using the coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenzotriazole (HOEt) and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, DMF, or mixtures thereof, at or near room temperature

for a period of 3 to 24h to provide the corresponding coupled product **5**, bearing the substituent N(R9)R10, where R9 and R10 are as defined above. Michael addition reactions can be achieved by the condensation of methyl vinyl ketone with the bicyclic **5** by heating in an organic acid, such as acetic acid, to yield a ketone product. Reductive amination under typical conditions of an appropriately substituted amine and a hydride source, such as sodium cyanoborohydride, sodium borohydride, zinc borohydride, lithium borohydride and the like, yields products such as **6**. Using classical Mannich chemistry an aminomethyl group can be introduced by treatment of **5** with a mixture of a suitably substituted amine (NH(A-R1)(R2)) and paraformaldehyde. In an organic acid such as acetic acid and the like and stirring at room temperature or heating between 40 and 100°C in this manner compounds such as **8** which correspond to the general structure (**A**) where Y represents CH₂ are formed. Alternatively, a two step procedure may be employed, where a Vilsmeier reaction, classically employing DMF and phosphorus oxychloride at a temperature between -10 °C and 25 °C, installs a formyl group at the 3-position of the imidazo[1,2-a]pyridine to give **7**. Reduction amination employing a suitably substituted amine [HN(-(A)-R1)R2] and a reducing agent such as sodium borohydride, sodium cyanoborohydride, zinc borohydride and the like, under acid or neutral conditions in a suitable solvent such as methylene chloride, chloroform, benzene, toluene and alcohols such as ethanol and the like, yields the 3-aminomethyl-imidazo[1,2-a]pyridines (**8**).

20

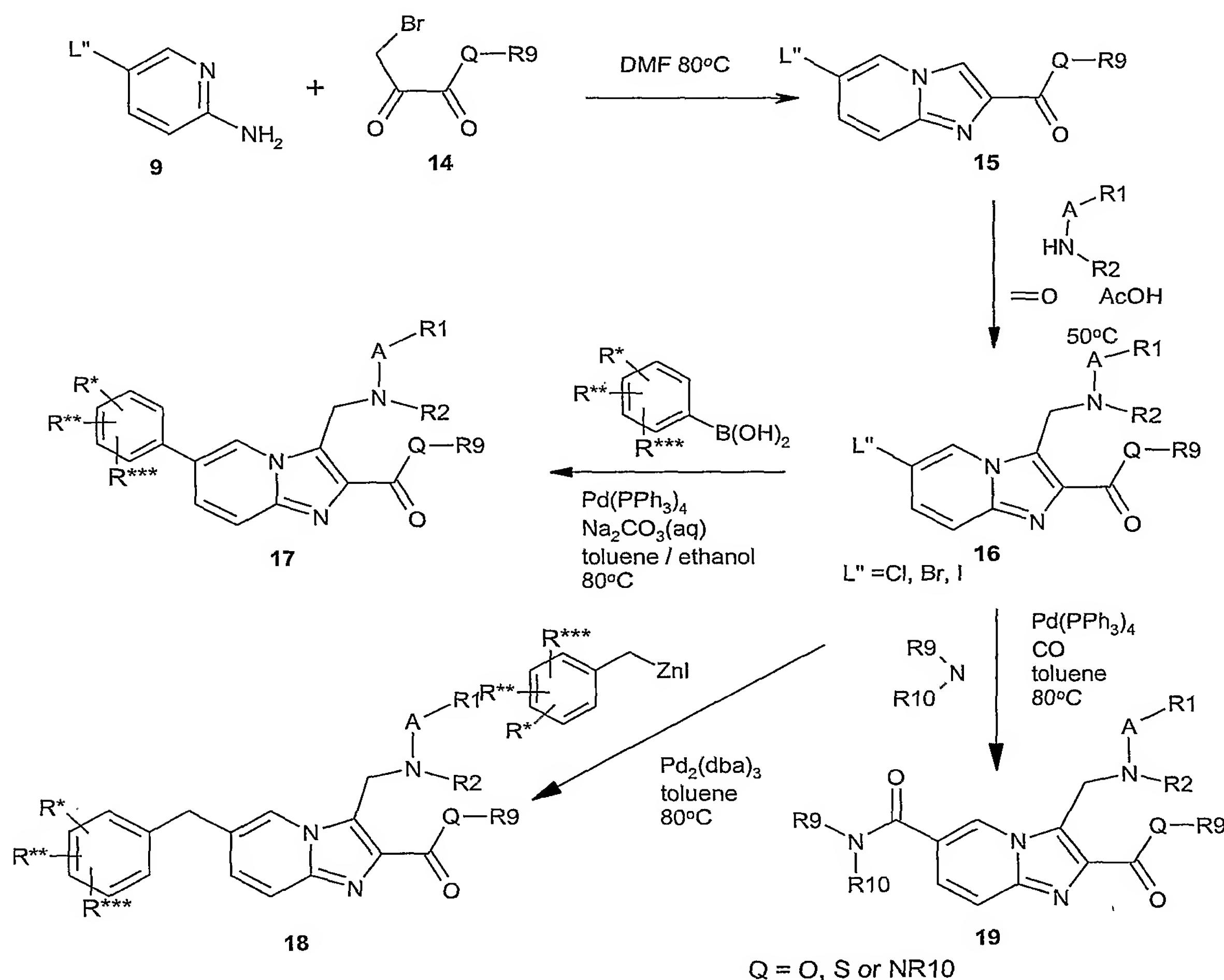
As an alternative to N(R9)R10, one can use R9OH in scheme b.



Scheme c

For example, Scheme c shows another general synthesis of 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridine commencing with commercially available 2-aminopyridines and 2'-bromoacetophenone. Thus, condensation of 2-aminopyridine **9** and a 2'-bromoacetophenone **3** under the preferred conditions noted above for the key cyclisation yields the bicyclic **10**. The Mannich reaction conditions described above for Scheme b again install the substituted aminomethyl group leading to the bicyclic **11**. Where **10** L' is chloride, bromide, iodide, O-trifluoromethanesulfonate, trialkyltin or like, **11** can be treated under palladium(0) catalysis with carbon monoxide at 1 atm or higher pressure in the presence of a substituted amine ($N(R9)R10$ as shown), alcohol ($R9OH$ – not shown) or thiol ($R9SH$ – not shown) in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like to yield 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridines such as **8**. Where **10** L' is chloride, bromide, iodide, O-trifluoromethanesulfonate, trialkyltin or like **11** can be treated under palladium(0), a weak base such aqueous sodium carbonate and the

like and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.,-H *Chem. Sci.* **1986**, *26*, 311-314), in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours, to give the imidazo[1,2-*a*]pyridine **12**. Similarly coupling of an arylalkylzinc iodide with **11** can be achieved using the methods of Negishi (e.g. Jackson, R. F. W.; James, H.; Wythes, M. J.; Wood, A. *J. Chem. Soc. Chem. Commun.* **1989**, 644) to yield imidazo[1,2-*a*]pyridines (**13**).
5

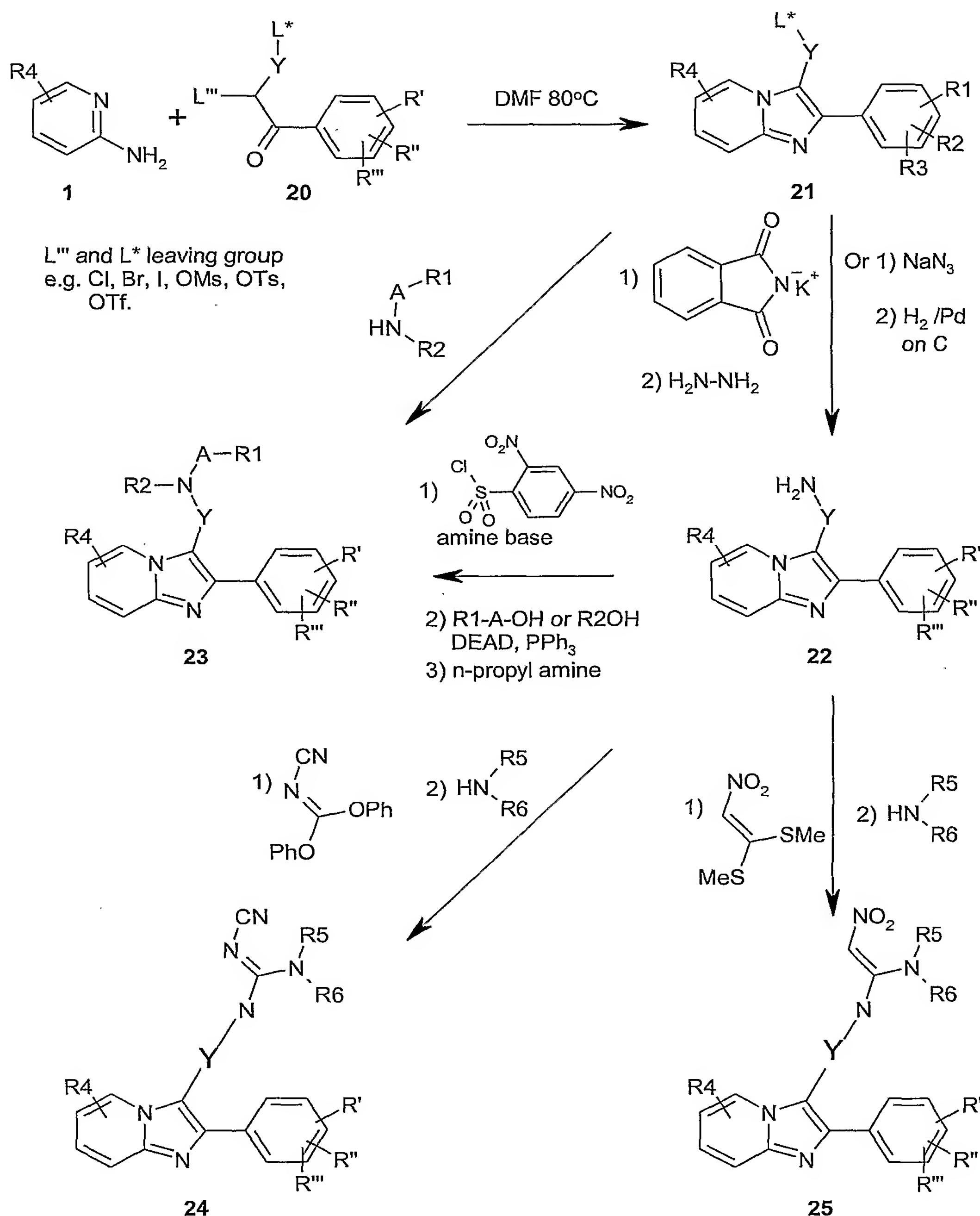


Scheme d

Condensation of a suitable substituted 2-aminopyridine **9** with a bromopyruvate **14** using the condition described above, yields 2-carboxyimidazo[1,2-*a*]pyridines **15**. With same chemical sequences of Mannich reaction then palladium catalysed carbonylation,

Suzuki couplings or Negishi couplings the 2-carboxyimidazo[1,2-*a*]pyrimidines **17**, **18** and **19** can be synthesised (Scheme d).

As an alternative to N(R9)R10, one can use R9OH in scheme d.

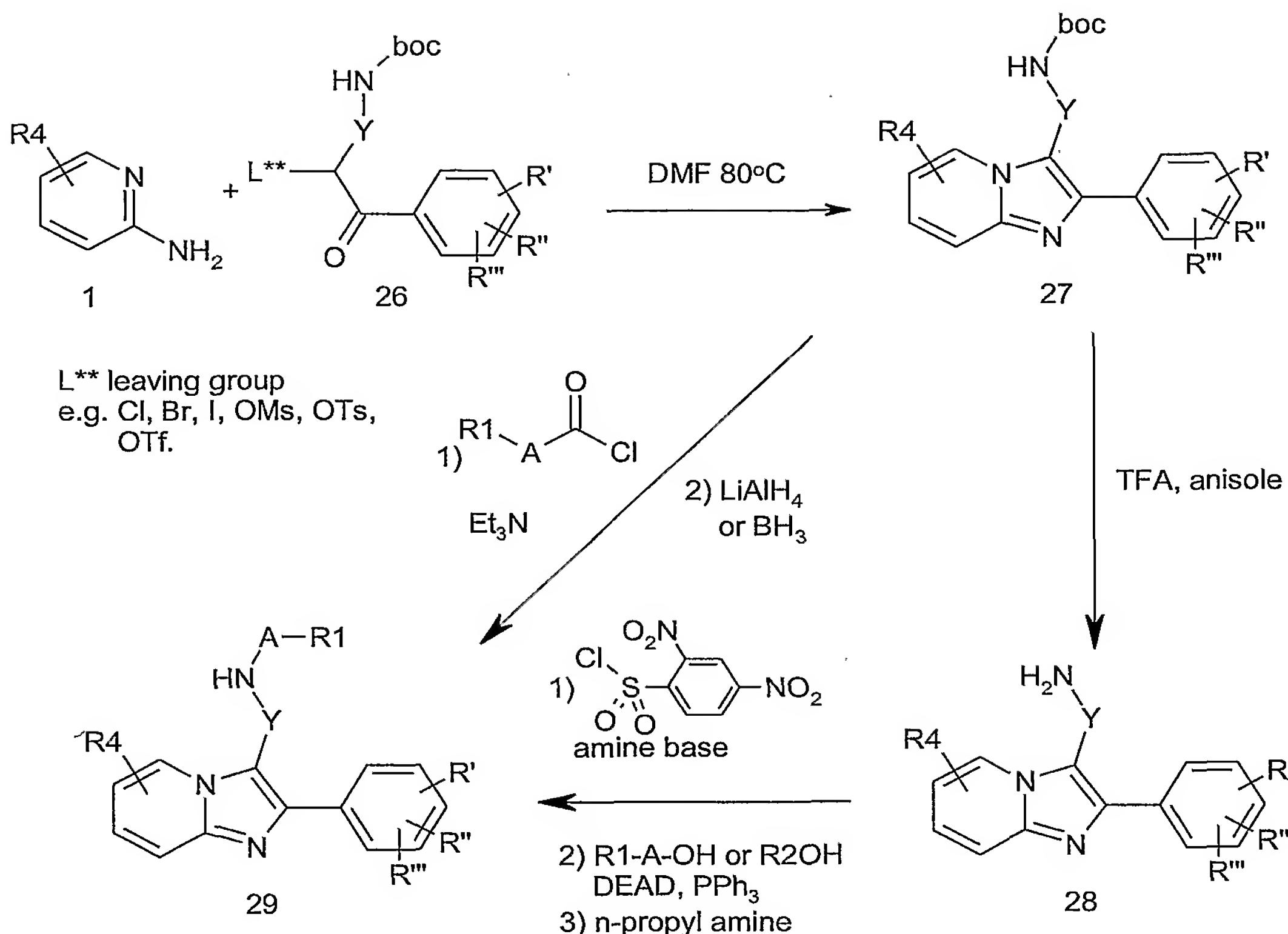


Scheme e.

Condensation of a suitable 2-aminopyridine **1** and a substituted aryl ketone **20** using the conditions described above gives imidazo[1,2-*a*]pyridines of the type **21** where a 3-position is already substituted with an alkyl chain. The leaving group L^* can be converted

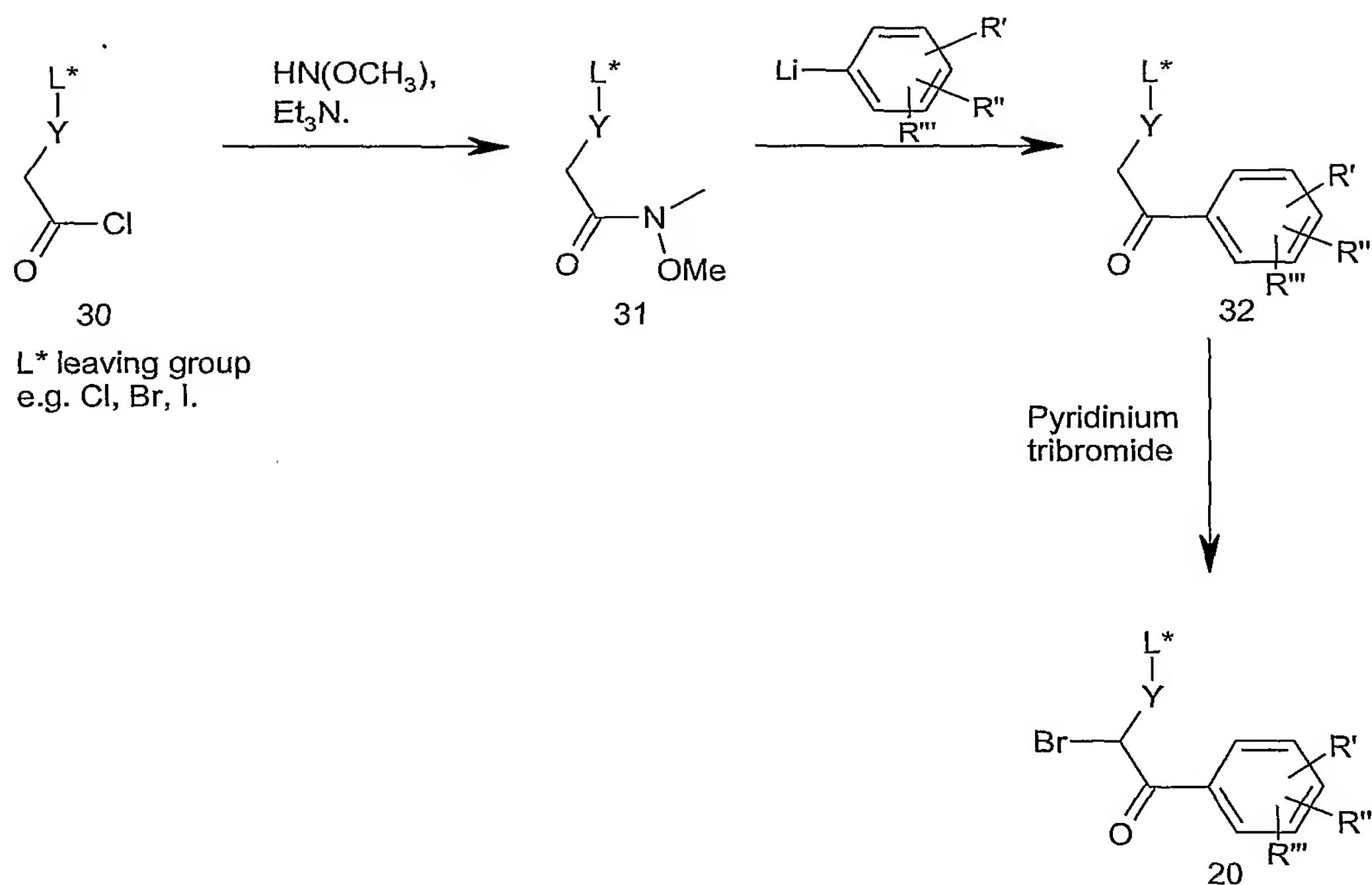
to an amine (**22**) by either the two step route of :- displacement with potassium phthalimide (heating in a suitable inert solvent such as DMSO, DMF or THF and mixtures thereof, and the like) then removal of the phthalimide protecting group (treatment with hydrazine in an inert solvent e.g. methylene chloride, chloroform, THF and mixtures thereof and the like), or displacement with sodium azide (heating in a suitable solvent DMSO, DMF or THF and mixtures thereof and the like) then reduction of the resultant azide (by treatment with hydrogen gas at atmospheric pressure or under high pressure [up to 600 psi] under palladium catalysis, or by Stoedinger reduction with triphenylphosphine). Groups R1 and R2 can be introduced by a modified Mitsunobu reaction. Reaction with an arylsulfonyl chloride such as 2-nitrobenzenesulphonyl chloride, 4-nitrobenzenesulphonyl chloride, 2,4-nitrobenzenesulphonyl chloride and a hindered amine base such as 2,4,6-collidine, 2,6-lutidine or the like in an inert organic solvent such as methylene chloride, provides the corresponding sulfonamide. Mitsunobu coupling of the sulfonamide and an alcohol (R₁OH or R₂OH) can be achieved by treatment with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyl diazocarboxylate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the dialkylated sulfonamide adduct. Removal of the sulfonamide group is accomplished by treatment with a nucleophilic amine such as *n*-propylamine to give substituted amine **23**.

The primary amine **22** can be converted to a cyano-guanidine (**24**) by the two step process of reaction with diphenyl cyanocarbonimidate in an inert organic solvent such as methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by condensation with an appropriately substituted amine (HNR₅R₆) in an inert organic from the list above. Similarly, reaction with 1,1'-bis(methylthio)-2-nitroethylene in an inert solvent such methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by condensation with an appropriately substituted amine (HNR₅R₆) in an inert organic solvent from the list above yields the nitroethyleneimidazo[1,2-*a*]pyridine **25**.



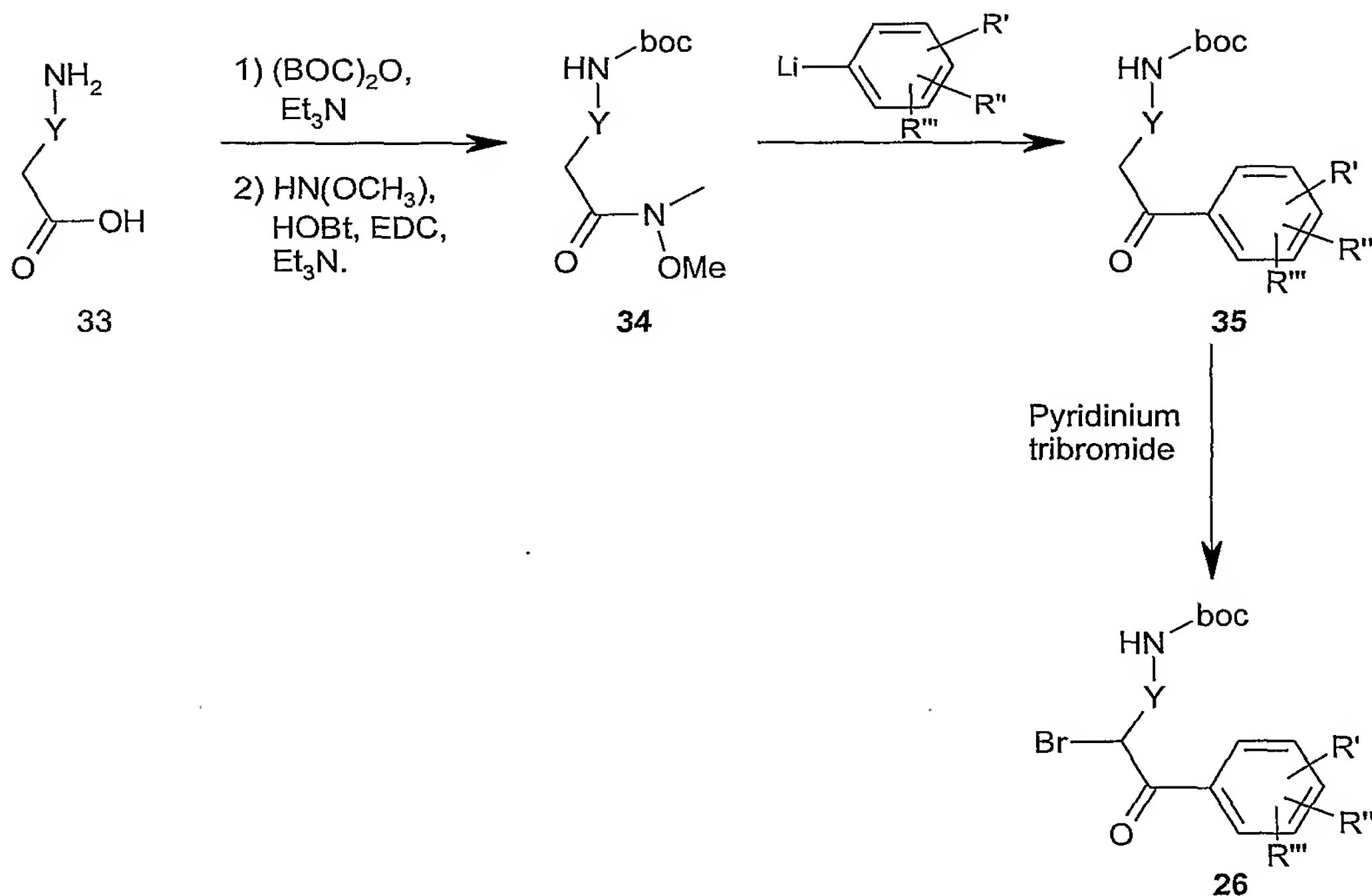
Scheme f

Condensation of 2-aminopyridines **1** with ketones bearing a *t*-butylcarbamate protected nitrogen atom (**26**) produces imidazo[1,2-*a*]pyridines such as **27**, where the nitrogen atom is already installed (Scheme f). The *t*-butylcarbamate protecting group is removed by treatment with an organic acid such as trifluoroacetic acid and the like, in the presence of a carbocation scavenger such as anisole, to yield the same imidazo[1,2-*a*]pyridines **28** as in scheme f. In the same manner the substitutents on the nitrogen atom can be installed by the Mitsunobu strategy (**28**→**29**) or by condensation with an acid chloride in the presence of a hindered amine base such as triethylamine, in an inert solvent such as methylene chloride, then reduction of this product with lithium aluminium hydride, in an inert solvent such as tetrahydrofuran, or by reduction with borane in a similarly inert solvent (**27**→**29**).



Scheme g.

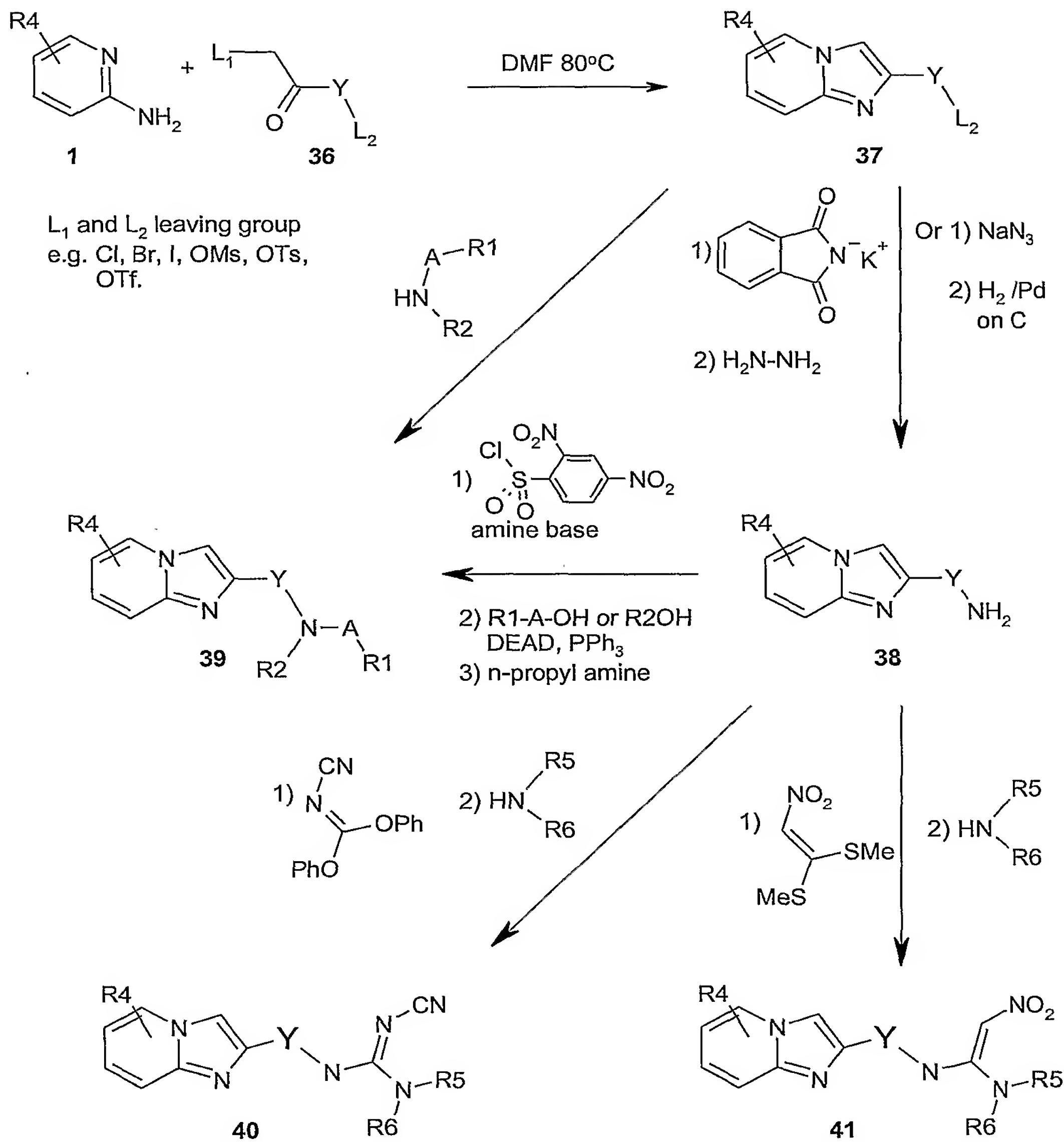
Substituted ketones (**20**) can be prepared, as outlined in Scheme g starting from appropriate acid chlorides such as **30**. Treatment of the acid chloride with N,N -dimethylhydroxylamine in the presence of an amine base such as triethylamine, and a suitable solvent such as methylene chloride at a temperature of -10 °C to 25 °C, yields the amide **31**. Further reaction with a substituted aryl organolithium (prepared essentially as described in Wakefield B, J.; *Organolithium Methods* Academic Press Limited, 1988, pp. 27-29 and references therein) in an inert solvent such as tetrahydrofuran, diethyl ether, benzene, toluene or mixture thereof and the like, at a temperature between -100 °C and 0 °C then quenching of the reaction mixture with a mineral acid such as hydrochloric acid, yields the aryl ketone **32**. Finally treatment of **32** with a bromine source such as pyridinium tribromide or pyrrolidone hydrobromide in an inert solvent such as chloroform or methylene chloride at -10 °C to 25 °C, yields a bromoketone **20** which is appropriate for the formation of an imidazo[1,2-*a*]pyridine.



Scheme h.

Commencing with a readily available amino acid with a suitable chain length for Y (33), the nitrogen atom can be installed directly by the route shown in Scheme h. Protection of the amine group of 33 with a *tert*-butylcarbamate group is achieved by condensation with di-*tert*-butyl dicarbonate in the presence of an amine base, for example triethylamine, in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature of -10 °C to 25 °C.

Coupling of the acid product with *N,N*-dimethylhydroxylamine in the presence of a coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenotriazole (HOEt), and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, dimethylformamide, or mixture thereof, at or near room temperature for a period of 3 to 24 h provided the corresponding coupled product 34. Following the same route described above for scheme g, the aryl group can then be installed and subsequently the α-bromo group to give the ketone 26, which is suitable for condensation with a 2-aminopyridine.

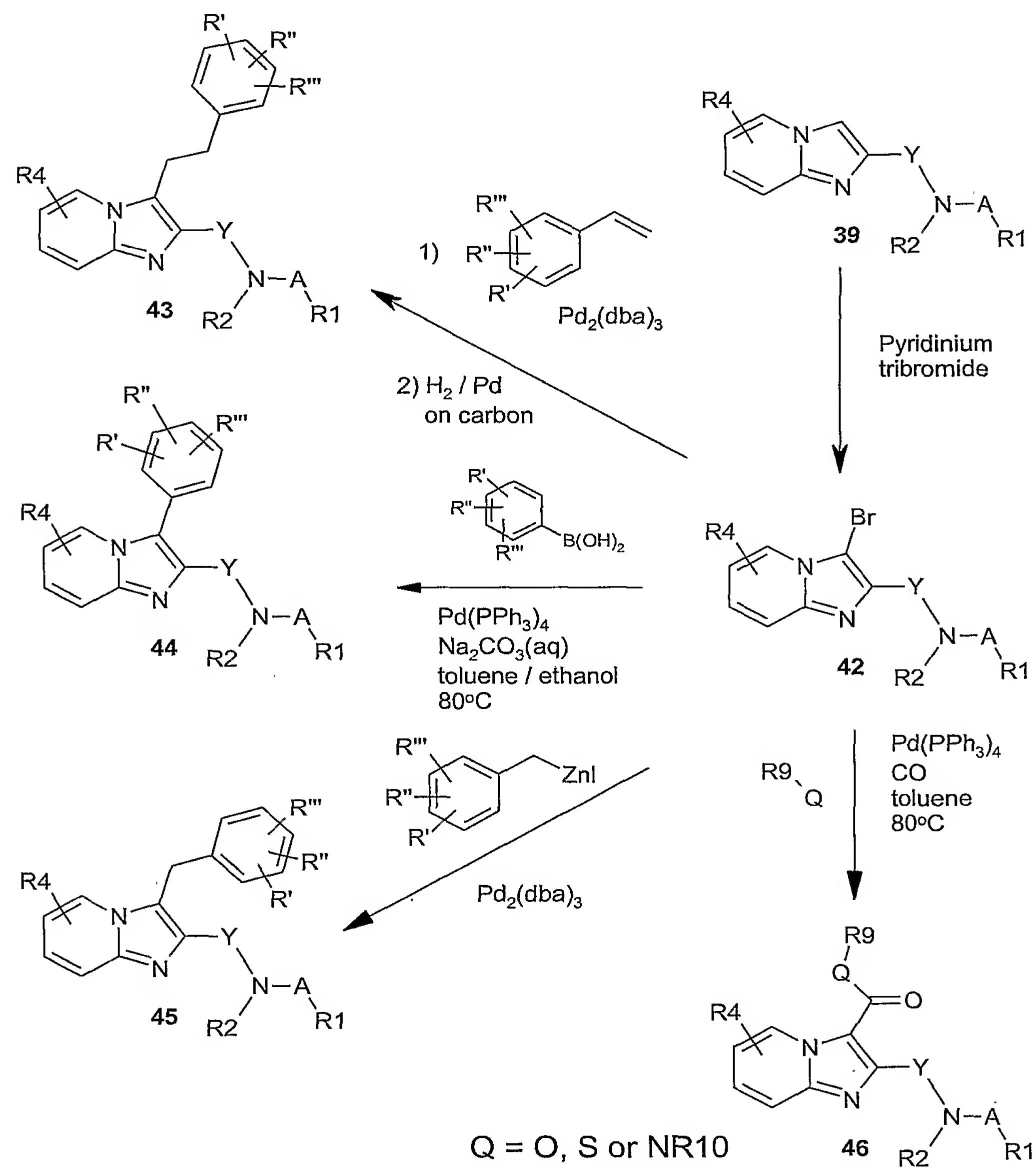


Scheme j

An isomeric series of imidazo[1,2-*a*]pyridines can be synthesised as described in Scheme j. Condensation of a suitably substituted 2-aminopyridine 1, under the general conditions described above, with a ketone bearing two leaving groups α to the carbonyl (36) yields an imidazo[1,2-*a*]pyridine such as 37. The substituted amino group can be installed by direct alkylation to yield 39, or by an indirect multistep route as shown above

in scheme j (compound 37 to compound 38 via intermediate 39), both routes are analogous to those shown in Schemes e.

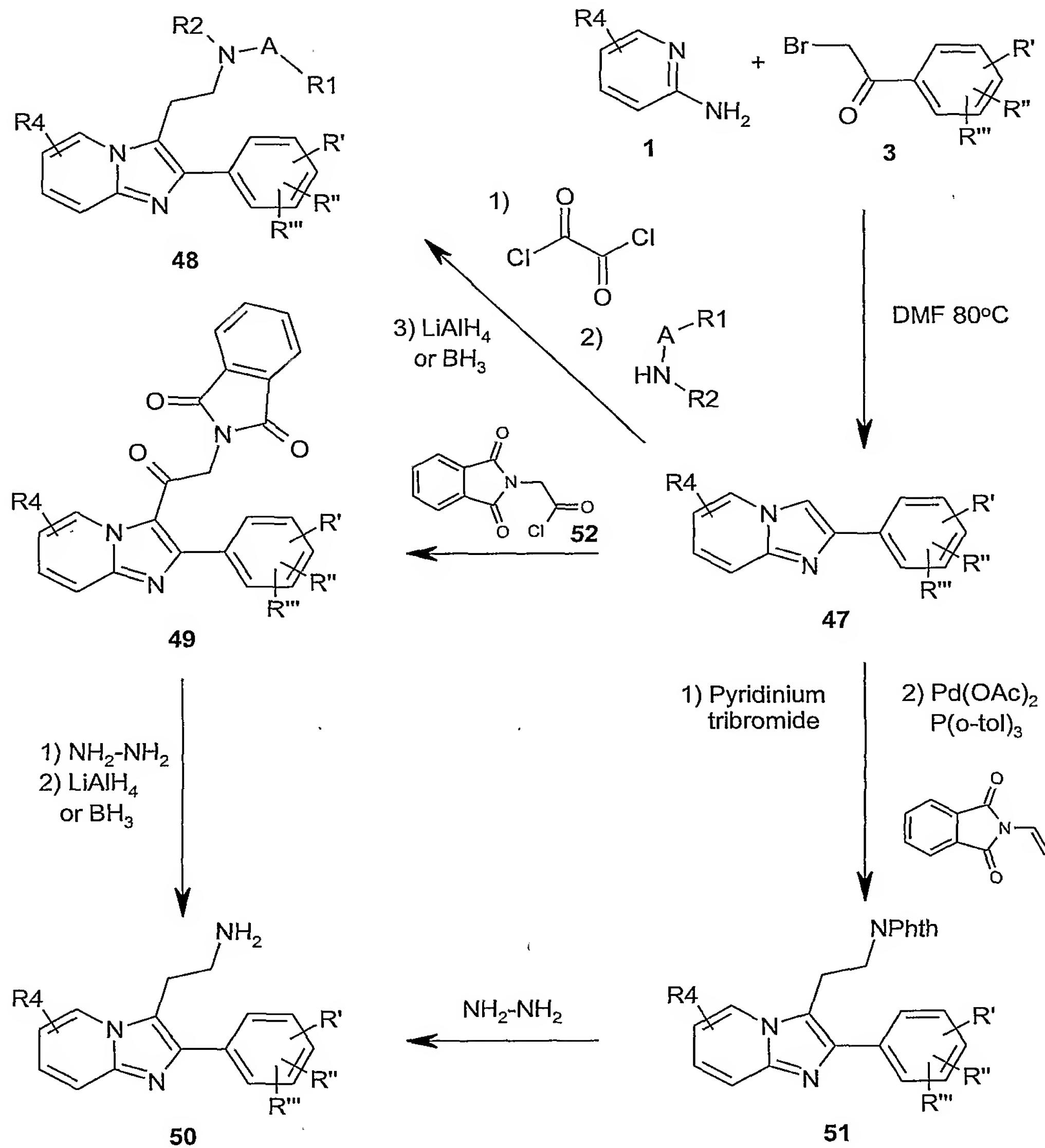
In addition the amine group can be elaborated further to a cyano-guanidine 40 or a nitroethylene moiety such as compound 41 by the same methods as described in Scheme e.



Scheme k.

Treatment of the imidazo[1,2-*a*]pyridine **39** with molecular bromine, pyridinium tribromide, poly (vinyl pyridinium tribromide) or pyrrolidone hydrobromide in an inert solvent such as chloroform or methylene chloride at -10 °C to 25 °C installs a bromo group at the two position (**42**). The compound QR9 is suitable for palladium (0) catalysed reactions, for example treatment with carbon monoxide at 1 atm or higher pressure in the presence of a substituted amine (Q=NR10), alcohol (Q=O) or thiol (Q=S) in an inert solvent such as toluene, benzene, dioxane, THF and the like, yields 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridines such as **46**. Again, treatment under palladium(0) catalysis with a weak base such aqueous sodium carbonate and the like and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y., *H Chem. Sci.* **1986**, *26*, 311-314.) in an inert solvent such as toluene, benzene, dioxane, THF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours to give the imidazo[1,2-*a*]pyridine **44**.

Similarly coupling of an arylalkylzinc iodide with **42** can be achieved using the method of Negishi (e.g. Jackson, R. F. W.; James, H.; Wythes, M. J.; Wood, A. *J. Chem. Soc. Chem. Commun.* **1989**, 644) yields imidazo[1,2-*a*]pyridines (**45**). Finally a Heck coupling reaction can be achieved using palladium (0) and a vinyl substituted aromatic compound in the presence of an organic amine base such as triethylamine and the like, in an inert solvent such as toluene, benzene, dioxane, THF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours to give the imidazo[1,2-*a*]pyridine **43**.



Scheme m.

Condensation of a suitable substituted 2-aminepyridine **1** with a bromoacetophenone **3** under the described conditions above, yields imidazo[1,2-*a*]pyridines such as **47**. A 5 ethylamine group can be installed in several ways to yield compounds described by structure **50**. Reaction **47** with oxalylchloride in an inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature between 0°C and 100°C, with or without the presence of an organic base, such as triethylamine, pyridine and the like, yields an acid chloride, which may be reacted 10 *in-situ* by treatment with an appropriately substituted amine [HN(R2)-A-R1] in the

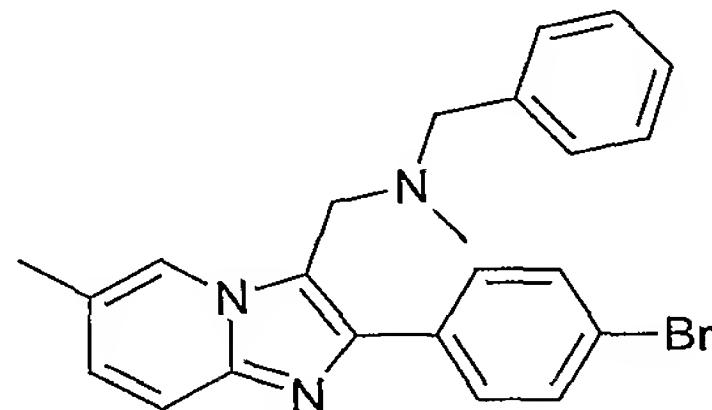
presence of an organic base such as triethylamine, pyridine and the like. The amide product from this step can then be reduced by an appropriate hydride reducing agent such as lithium aluminium hydride or borane in an appropriate inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran, thus, a fully substituted compound such as **48** can be synthesised.

Treatment of **47** with acid chloride **52** [prepared as described by Hubschwerlen, C.; Specklin, J.-L; *Org. Synth.* 1993, 73, 14] in an inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature between 0°C and 100°C, with or without the presence of an organic base, such as triethylamine, pyridine and the like, yields the imidazo[1,2-*a*]pyridines **49**. Removal of the phthalimide protecting group by treatment with hydrazine, then reduction of the carbonyl group by an appropriate hydride reducing agent, such as lithium aluminium hydride or borane, in an appropriate inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran, yields the amine **50**, which may then be elaborated as shown in the earlier schemes.

Reaction of imidazo[1,2-*a*]pyridines **47** with a bromine source such as pyridinium tribromide or pyrrolidone hydrobromide in an inert solvent such as chloroform or methylene chloride at -10 °C to 25 °C, yields 3-bromo substituted imidazo[1,2-*a*]pyridines, which in turn can be treated with *N*-vinylphthalimide using Heck coupling conditions of palladium (0) catalysis in the presence of an organic amine base such as triethylamine and the like, in an inert solvent such as toluene, benzene, dioxane, THF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours to give the imidazo[1,2-*a*]pyridine **51**. Finally treatment with hydrazine under standard conditions yields the 3-ethylamine imidazo[1,2-*a*]pyridine **50**, which again may be elaborated as shown in the earlier schemes.

EXAMPLES**Example A1 - Preparation of N-Benzyl-N-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine.**

5

**Step A1: 2-(4-bromophenyl)-5-methyl-imidazo[1,2-a]pyridine.**

10 A mixture of 2-amino-5-picoline (2.00 g 18.5 mmol) and 2,4'-dibromoacetophenone (5.10 g 18.5 mmol) in DMF (20 mL) was heated at 80 °C for 1h 45 min. The mixture was cooled to RT then diluted with water (200 mL) and basified with 2M NaOH (aq) (150 mL). The mixture was extracted into EtOAc (2 × 200mL) and the extracts dried (MgSO_4) and concentrated *in vacuo* to give the crude title compound as a yellow solid (5.12 g 96%).

15 **Mass Spectrum:** m/e $\text{C}_{14}\text{H}_{12}\text{BrN}_2$ ($\text{M}+\text{H}$) 287.37 and 289.38 found.

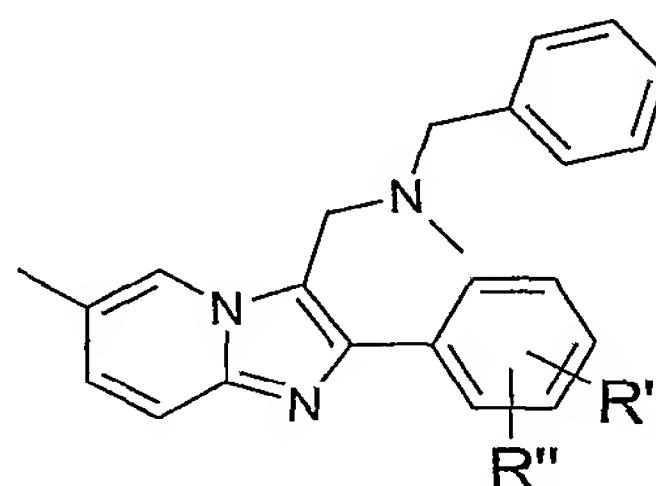
$^1\text{H NMR spectrum (DMSO-d}_6\text{):}$ δ $^1\text{H NMR}$ (300 MHz, D6 -DMSO) 2.27 (3H, s); 7.11 (1H, d); 7.48 (1H, d); 7.61 (2H, d); 7.90 (2H, d); 7.94 (1H, s); 8.32 (1H, s).

Step A2:N-Benzyl-N-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine.

20 A mixture of 2-(4-bromophenyl)-5-methyl-imidazo[1,2-a]pyridine(4.96 g 17.3 mmol), paraformaldehyde (518 mg 17.3 mmol) and benzylmethylamine(2.23 mL 17.3mmol) in acetic acid (9 mL) was heated for 2h at 60 °C. The majority of the solvent was removed *in vacuo* and the mixture rediluted with EtOAc (400 mL) and washed with 2M NaOH (aq) (2 × 150mL). The solution was dried (MgSO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient neat CH_2Cl_2 to 6% MeOH) gave the title

compound as an orange oil (3.86 g 53%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether (23 mL) to a solution of the title compound in EtOAc (4 mL). The salt was precipitated with diethyl ether and collected by centrifuge.

5 Following a procedure similar to that described in Example 1, the following compounds were prepared.



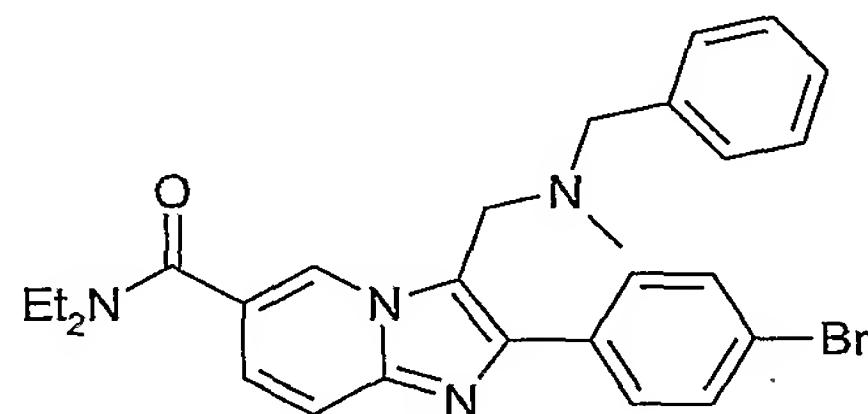
Example No.	R'	R''	δ 1H NMR (300 MHz D6-DMSO)	m/e (ESP+) (MH+)
A1 <u>N-Benzyl-N-methyl-2-(4-</u> <u>bromophenyl)-3-</u> <u>methylamino-5-</u> <u>methylimidazo[1,2-</u> <u>a]pyridine.</u>	4-Br	H	2.04 (3H, s); 2.31 (3H, s); 3.52 (2H, s); 3.96 (2H, s); 7.15 (1H, d); 7.20 - 7.30 (5H, m); 7.49 (1H, d); 7.63 (2H, d); 7.84 (2H, d); 8.31 (1H, s).	420 422
A2 <u>N-Benzyl-N-methyl-2-(4-</u> <u>chlorophenyl)-3-</u> <u>methylamino-5-</u> <u>methylimidazo[1,2-</u> <u>a]pyridine</u>	4-Cl	H		362 364
A3	4-F	H	2.40 (3H, s), 2.47 (3H, s),	360

<u>N-Benzyl-N-methyl-2-(4-fluorophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine</u>			4.20 (1H, s), 4.55 (1H, s), 5.00 (2H, s), 7.38-7.57 (6H, m), 7.86-7.97 (m, 4H), 9.15 (0.5H, s) and 11.64 (0.5H, s).	
A4	4-CN	H	2.41 (3H, s), 2.44 (3H, s), 4.23 (1H, s), 4.53 (1H, s), 5.02 (2H, s), 7.43 (3H, s), 7.54 (2H, s), 7.73 (1H, d), 7.85 (1H, d), 8.02 (4H, s), 8.92 (0.5H, s) and 11.17 (0.5H, s).	367
<u>N-Benzyl-N-methyl-2-(4-cyanophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine</u>				
A5	4-OMe	H	2.40 (3H, s), 2.47 (3H, s), 3.86 (3H, s), 4.20 (1H, s), 4.54 (1H, s), 5.00 (2H, s), 7.16 (2H, d), 7.42 (3H, s), 7.55 (2H, s), 7.75 (2H, d), 7.91 (2H, s), 9.05 (0.5H, s) and 11.47 (0.5H, s).	372
<u>N-Benzyl-N-methyl-2-(4-dimethoxyphenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine</u>				
A6	4-OMe	3-OMe	2.39 (3H, s), 2.48 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 4.24 (1H, s), 4.57 (1H, s), 5.03 (2H, s), 7.14 (1H, d), 7.37 (2H, d), 7.41 (3H, s), 7.92 (2H, s), 9.08 (0.5H, s) and 11.50 (0.5H, s).	402
<u>N-Benzyl-N-methyl-2-(3,4-dichlorophenyl)-3-</u>				
A7	4-Cl	3-Cl	2.37 (3H, s), 2.46 (3H, s), 4.12 (1H, s), 4.54 (1H, s), 4.70 (2H, s), 4.87 (1H, s),	410
<u>N-Benzyl-N-methyl-2-(3,4-dichlorophenyl)-3-</u>				412

<u>methylamino-5-</u>			7.42 (3H, s), 7.53 (2H, S),	
<u>methylimidazo[1,2-</u>			7.67 (1H, d), 7.70 (1H, d),	
<u>a]pyridine</u>			7.85 (1H, d), 7.94 (2H, s), 9.06 (0.5H, s) and 11.44 (0.5H, s).	

Example B1 - Preparation of N-Benzyl-N-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-a]pyridine.

5



Step B1: 2-(4-bromophenyl)-5-carboxy-imidazo[1,2-a]pyridine.

10 A mixture of 6-aminonicotinic acid (1.00 g 7.24 mmol) and 2,4'-dibromoacetophenone (4.02 g 14.5 mmol) in DMF (10 mL) was heated at 60 °C for 24 h. The mixture was cooled to RT then partitioned between water (200 mL) and EtOAc (250mL). The yellow precipitate between the two layers was removed by filtration and dried by high vacuum to yield the title compound (1.72 g 75%).

15 **Mass Spectrum:** m/e C₁₄H₁₀BrN₂O₂ (M+H) 317.16 and 319.16 found.

Step B2: 2-(4-bromophenyl)-5-diethylamido-imidazo[1,2-a]pyridine.

HOBT (426 mg 3.15mmol) was added in one portion to a stirred solution of 2-(4-bromophenyl)-5-carboxylic-imidazo[1,2-a]pyridine (1.00 g 3.15 mmol) and EDC (605 mg 3.15 mmol) in CH₂Cl₂ (30 mL) under N₂ at 0°C. The mixture was stirred for 1h then

diethylamine (1.63 mL 15.8 mmol) was added and the mixture allowed to stir at RT for 20h. After this time the solvent was removed *in vacuo* then the mixture rediluted with EtOAc (250 mL) then washed with 1M citric acid (200 mL) then saturated NaHCO₃ (aq) (200 mL) and brine (200 mL). The organic solution was dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a yellow solid (601 mg 51%).

Mass Spectrum: m/e C₁₈H₁₈BrN₂O₂ (M+H) 272.20 and 274.23 found.

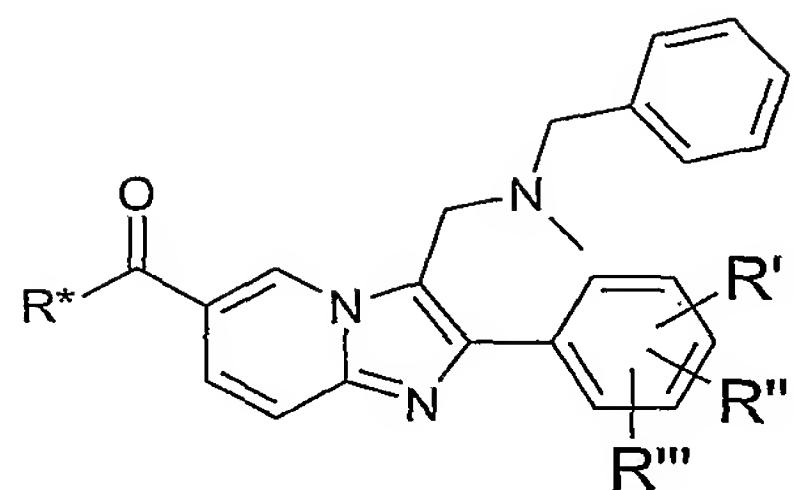
¹H NMR spectrum (DMSO-d₆): δ ¹H NMR (300 MHz, D₆ -DMSO) 1.15 (6H, t), 3.18 (4H, m); 7.12 (1H, d); 7.30 (1H, d); 7.33 (2H, d); 7.93 (2H, d); 8.44 (1H, s); 8.68 (1H, s).

10

Step B3: N-Benzyl-N-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-a]pyridine.

A mixture of 2-(4-bromophenyl)-5-diethylamido-imidazo[1,2-*a*]pyridine (300 mg 0.806 mmol), paraformaldehyde (26.0 mg 0.812 mmol) and benzylmethylamine(100 μL 0.806 mmol) in acetic acid (2 mL) was heated for 1h at 50 °C. The majority of the solvent was removed *in vacuo* and the mixture rediluted with EtOAc (200 mL) and washed with 2M NaOH (aq) (2 × 150mL). The solution was dried (MgSO₄) and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient neat CH₂Cl₂ to 6% MeOH) gave the title compound as an yellow oil (276 mg 68%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether (150 μL) to a solution of the title compound in EtOAc (500 μL). The salt was precipitated with diethyl ether and collected by centrifuge.

25 Following a procedure similar to that described in Example 1, the following compounds were prepared.

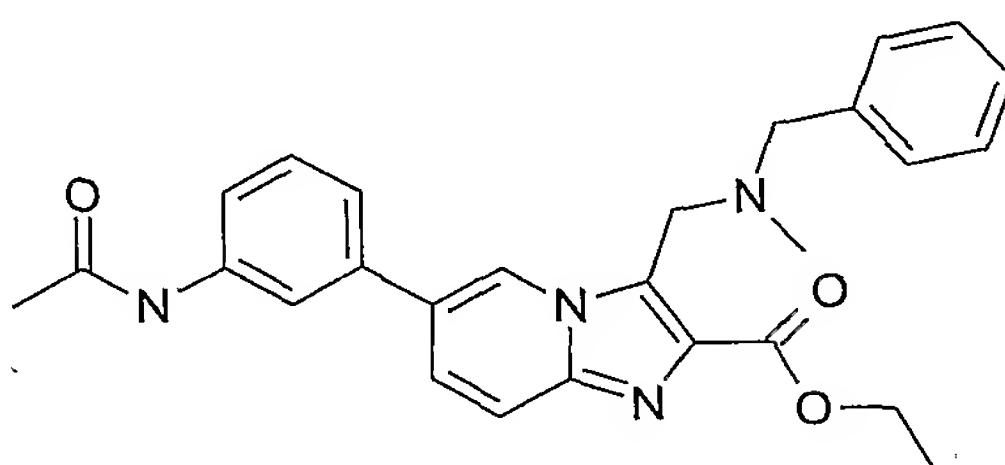


Example No.	R'	R''	R'''	R*	δ 1H NMR (300 MHz, D6 - DMSO)	m/e (M+H)
B1 <u>N-Benzyl-N-methyl-2-(4-</u> <u>bromophenyl)-5-diethylamido-3-</u> <u>methylamino-imidazo[1,2-</u> <u>a]pyridine</u>	4-Br	H	H	Et ₂ N	1.05 - 1.13 (6H, b); 2.04 (3H, s); 3.39 (4H, b); 3.50 (2H, s); 4.09 (2H, s); 7.16 - 7.29 (5H, m); 7.32 (1H, d); 7.62 (1H, d); 7.70 (2H, d); 7.86 (2H, d); 8.58 (1H, s).	505 507
B2 <u>N-Benzyl-N-methyl-2-(4-</u> <u>bromophenyl)-5-</u> <u>isopropoxycarbonyl-3-</u> <u>methylamino-imidazo[1,2-</u> <u>a]pyridine</u>	4-Br	H	H	iPrO	1.20 (6H, d); 1.98 (3H, s); 3.59 (2H, b); 4.15 (2H, s); 7.21 - 7.33 (5H, m); 7.62 - 7.74 (4H, m); 7.75 - 7.83 (4H, m); 9.25 (1H, s).	492 494
B3 <u>N-Benzyl-N-methyl-2-(4-</u> <u>isopropylamidophenyl)-5-</u> <u>isopropoxycarbonyl-3-</u> <u>methylamino-imidazo[1,2-</u>	4- NH C(O)iPr	H	H	iPrO	1.12 (6H, d); 1.38 (6H, d); 1.97 (3H, s); 2.64 (1H, 'q'); 3.57 (2H, s); 4.16 (2H, s); 5.21 (1H, 'q'); 7.20 -	499

<u>a]pyridine</u>					7.32 (5H, m); 7.63 (1H, d); 7.70 (1H, d); 7.75(4H, 's'); 9.28 (1H, s); 9.92 (1H, s).	
B4 <u>N-Benzyl-N-methyl-2-(3,4,5-trimethylphenyl)-5-diethylamido-3-methylamino-imidazo[1,2-a]pyridine</u>	3-Me, <u>N-Benzyl-N-methyl-2-(3,4,5-trimethylphenyl)-5-diethylamido-3-methylamino-imidazo[1,2-a]pyridine</u>	Me	4-Me	Et ₂ N	1.16 (6H, b); 2.20 (3H, s); 2.26 (3H, s); 2.37 (6H, s); 3.48 (4H, b); 3.54 (2H, s); 4.04 (2H, s); 7.18 - 7.32 (6H, m); 7.46 (2H, s); 7.63 (1H, d); 8.58 (1H, s).	469

Example C - Preparation of Ethyl N-benzyl-N-methyl-5-(3-acetamidophenyl)-3-methylamino-imidazo[1,2-a]pyridine-2-carboxylate.

5



Step C1: Ethyl 5-bromo-imidazo[1,2-a]pyridine-2-carboxylate.

10 A mixture of 2-amino-5-bromopyridine (1.00 g 5.78 mmol) and ethyl bromopyruvate (0.730 mL 5.78 mmol) in DMF (10 mL) was heated at 80 °C for 2 h. The mixture was cooled to RT then partitioned between water (200 mL) and EtOAc (250mL). The aqueous layer was extracted again with EtOAc (2 × 100mL) and the combined extracts dried

(MgSO₄) and concentrated *in vacuo* to yield the crude title compound as a yellow solid (1.24 g 80%).

Mass Spectrum: m/e C₁₀H₉BrN₂O₂ (EP+) (MH⁺) 264 and 271 found.

¹H NMR spectrum (DMSO-d₆): δ ¹H NMR (300 MHz, D₆ -DMSO) 1.31 (3H, t), 4.31

5 (2H, q); 7.46 (1H, d); 7.61 (1H, d); 7.33 (2H, d); 8.45 (1H, s); 8.89 (1H, s).

Step C2: **Ethyl N-Benzyl-N-methyl-5-bromo-3-methylamino-imidazo[1,2-a]pyridine-2-carboxylate.**

10

A mixture of ethyl 5-bromo-imidazo[1,2-a]pyridine-2-carboxylate (1.24 g 4.61 mmol), paraformaldehyde (138 mg 4.61 mmol) and benzylmethylamine(600 μL 4.61 mmol) in acetic acid (15 mL) was heated for 1h at 50 °C. The majority of the solvent was removed *in vacuo* and the mixture rediluted with EtOAc (250 mL) and washed with 2M NaOH (aq) (3 × 150mL). The solution was dried (MgSO₄) and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient neat CH₂Cl₂ to 10% MeOH) gave the title compound as an yellow oil (980 mg 53%).

Mass Spectrum: m/e C₁₉H₂₀BrN₃O₂ (EP+) (MH⁺) 264 and 271 found.

¹H NMR spectrum (DMSO-d₆): δ ¹H NMR (300 MHz, D₆ -DMSO) 1.32 (3H, t); 2.08

20 (3H, s); 3.58 (2H, s); 4.22 (2H, s); 4.33 (2H, q); 7.21 - 7.34 (5H, m); 7.50 (1H, d); 7.59 (1H, d); 8.57 (1H, s).

Step C3: **Ethyl N-benzyl-N-methyl-5-(3-acetamidophenyl)-3-methylamino-imidazo[1,2-a]pyridine-2-carboxylate.**

25

Tetrakis(triphenylphosphine) palladium(0) (58.0 mg 0.050 mmol) was added in one portion to a degassed mixture of ethyl N-Benzyl-N-methyl-5-bromo-3-methylamino-imidazo[1,2-a]pyridine-2-carboxylate (200 mg 0.498 mmol) and N-acetyl-3-aminobenzeneboronic acid (89.0 mg 0.498 mmol) in toluene (2 mL), ethanol (2 mL) and saturated NaHCO₃ (aq) (1 mL). The mixture was heated at 80 °C with vigorous stirring for

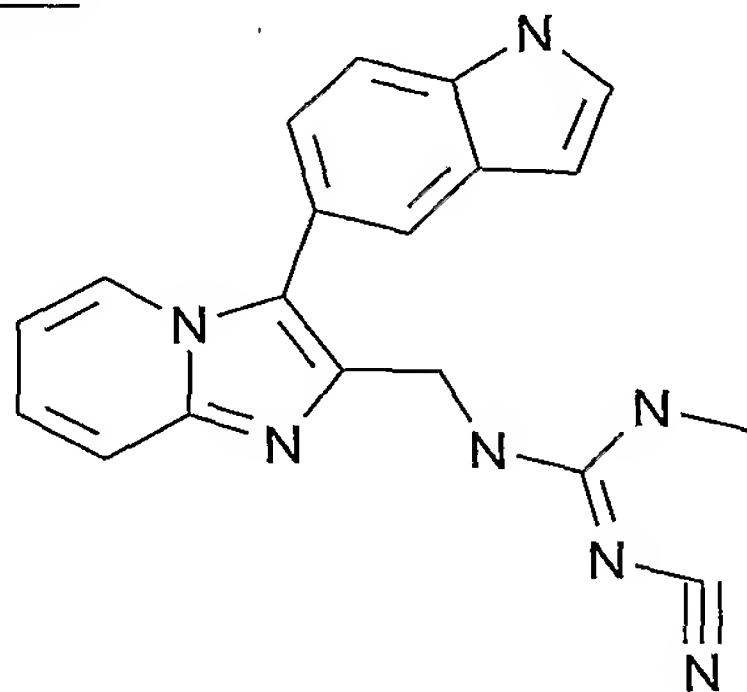
4 h then cooled to RT. The mixture was diluted with EtOAc (200 mL) and washed with water (100 mL) and brine (100 mL) then dried (MgSO_4). The solution was concentrated in vacuo and the product isolated by flash column chromatography (3 runs on silica slow gradient neat CH_2Cl_2 to 20% MeOH). This gave the title compound as a colourless oil (27.0 mg 12%).

Mass Spectrum: m/e $\text{C}_{27}\text{H}_{28}\text{N}_4\text{O}_3$ (EP⁺) (MH^+) 456 found.

¹H NMR spectrum (DMSO-d₆): δ ¹H NMR (300 MHz, CDCl_3) 1.46 (3H, t); 2.21 (3H, s); 2.25 (3H, s); 3.61 (2H, s); 4.23 (2H, s); 4.48 (2H, q); 7.15 - 7.29 (5H, m); 7.29 - 7.37 (1H, m); 7.38 - 7.49 (3H, m); 7.76 (1H, s); 7.89 (1H, s); 8.39 (1H, s).

HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether (177 μL) to a solution of the title compound in EtOAc (300 μL). The salt was precipitated with diethyl ether and collected by centrifuge.

Example D1 - Preparation of N-Cyano-N'-[3-(1H-indol-5-yl)-imidazo[1,2-a]pyridin-2-ylmethyl]-N''-methyl-guanidine



Step D1: Preparation of 1-Imidazo[1,2-a]pyridin-2-ylmethyl-3-cyano-2-phenyl-isourea

20

A mixture of 2-aminomethylimidazo[1,2-a]pyridine (1.20 g, 9.00 mmol) and diphenylcyanocarbonimidate (2.35 g, 9.90 mmol) in IPA were stirred at ambient temperature for 4 h. The cloudy reaction gave rise to a precipitate which was filtered. This was washed with

ether and dried to yield the title compound as a white solid (1.55 g, 59 %). Mass Spectrum: 292 [MH]⁺

5 **Step D2: Preparation of *N*-Cyano-*N'*-(imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N*"'-methyl-guanidine**

A mixture of 1-imidazo[1,2-*a*]pyridin-2-ylmethyl-3-cyano-2-phenyl-isourea (1.00 g, 3.40 mmol) and excess methylamine in 33% aq. ethanol (5 mL) in IPA were warmed to 70 °C for 2 h. The reaction was concentrated *in vacuo*, and the residue triturated with ethyl acetate and filtered. The resulting solid was washed with ether and dried to give the title compound as a white solid (0.75 g, 97%).

10 Mass Spectrum: 229 [MH]⁺

15 ¹H NMR spectrum (DMSO-d₆): 2.72 (3H, s); 4.40 (2H, s); 6.82 (1H, t); 7.17 (1H, brs), 7.19 (1H, t); 7.40 (1H, br s); 7.48 (1H, d); 7.78 (1H, s); 8.48 (1H, d).

15

Step D3: *N*-Cyano-*N'*-(3-bromo-imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N*"'-methyl-guanidine

A mixture of *N*-Cyano-*N'*-(imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N*"'-methyl-guanidine (0.300 g, 1.30 mmol), poly(4-vinylpyridinium tribromide) (0.467 g, 1.40 mmol), pyridine (2 drops) in CH₂Cl₂ were stirred at ambient temperature for 16 h. DMF was added, the solid support filtered off, and the mother liquors concentrated *in vacuo*. The residue was triturated with CH₂Cl₂ and the resulting solid filtered to yield the title compound as a fawn solid (0.390 g, 98%).

25 Mass Spectrum: 307, 309 [MH]⁺

¹H NMR spectrum (DMSO-d₆): 2.76 (3H, d); 4.46 (2H, d); 7.21 (1H, d); 7.24 (1H, t); 7.45 (1H, t); 7.58 (1H, t); 7.76 (1H, d); 8.45 (1H, d)

Step D4: Preparation of *N*-Cyano-*N'*-[3-(1H-indol-5-yl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N*''-methyl-guanidine

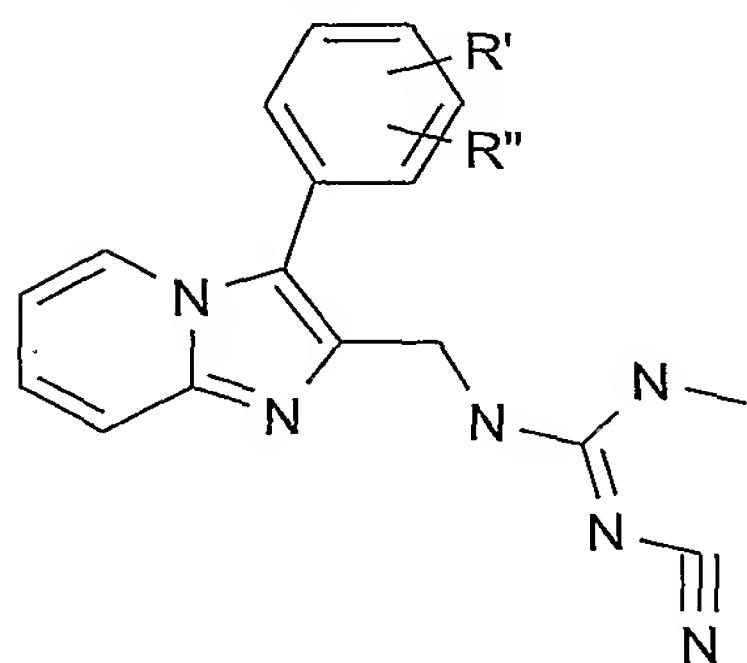
To a mixture of *N*-Cyano-*N'*-(3-bromo-imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N*''-methylguanidine (700 mg, 0.230 mmol), 5-indolyl boronic acid (560 mg, 0.345 mmol), saturated Na₂CO₃ (1.5 mL), ethanol (0.60 mL) and toluene (3 mL) was added a catalytic amount of Pd(PPh₃)₄. The reaction was stirred at 80 °C for 16 h. The reaction was poured onto a hydromatrix column and eluted with CH₂Cl₂. Flash column chromatography (silica gel, slow gradient, neat CH₂Cl₂ to 5% MeOH:CH₂Cl₂) gave the title compound as a white solid (17.0 mg, 22%).

Mass Spectrum: 344 [MH]⁺

¹H NMR spectrum (DMSO-d₆): 2.89 (3H, d); 4.02 (2H, d); 5.85 (1H, t); 6.63 (1H, s); 6.88 (1H, t); 7.17- 7.27 (3H, m); 7.36 (1H , m); 7.57 (1H, d); 7.59 (1H, d); 7.66 (1H, s), 8.08 (1H, d); 8.78 (1H, br s)

15

Following a procedure similar to that described for Example D1, the following compounds were prepared.



Example No.	R'	R''	¹ H NMR spectrum (DMSO-d ₆):	Mass Spectrum [MH] ⁺
D2	3-OMe	4-OMe	2.71(3H, d); 3.80 (3H, s); 3.86 (3H,	365

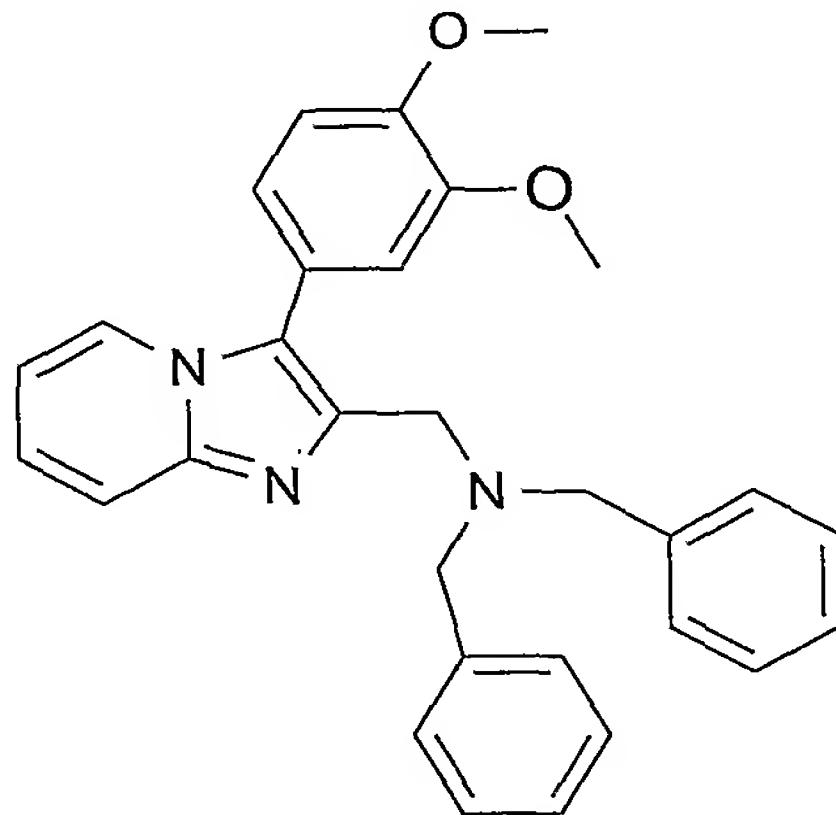
			s); 4.55 (2H, d); 7.21 (2H, s); 7.28 (2H, s) ; 7.43 (1H, t); 7.65 (1H, t); 7.90-8.03 (2H, m); 8.50 (1H, d)	
D3	4-Cl		2.69 (3H, d); 4.54 (2H, d); 7.30 (1H, d); 7.45 (1H, t); 7.73 (4H, s); 7.92-8.08 (3H, m); 8.52 (1H, d)	339
D4	3-Me	5-Me	2.41 (6H, s); 2.92 (3H, d); 4.42 (2H, d); 5.78 (1H, t); 6.81 (1H, t); 7.03 (2H, s); 7.15 (1H, s); 7.22 (2H, t); 7.57 (1H, d); 8.04 (1H, d)	333

D2 = *N*-Cyano-*N'*-[3-(3,4-dimethoxyphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine

5 **D3 = *N*-Cyano-*N'*-[3-(4-chlorophenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine**

D4 = *N*-Cyano-*N'*-[3-(3,5-dimethylphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine

Example E - N,N-Dibenzyl-2-methylamino-3-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridine



5 **Step E1: Preparation of *N,N*-Dibenzyl-2-methylaminoimidazo[1,2-a]pyridine**

A mixture of 2-aminoethylimidazo[1,2-a]pyridine dihydrochloride (0.500 g, 2.26 mmol), benzyl bromide (0.430 g, 2.50 mmol) and powdered K₂CO₃ (1.56 g, 11.3 mmol) in DMF (20 mL) was heated at 100 °C for 2 h. The DMF was removed *in vacuo* and then residue taken into CH₂Cl₂ and filtered to remove inorganics. This was purified by flash column chromatography (silica gel, CH₂Cl₂ to 5% MeOH:CH₂Cl₂) to give the title compound as orange oil (0.405 g, 55%).

Mass Spectrum: 328 [MH]⁺

¹H NMR spectrum (CDCl₃): 3.68 (4H, s); 3.82 (2H, s); 6.74 (1H, t); 7.10 (1H, t); 7.18-15 7.48 (10H, m); 7.55 (1H, d); 7.60 (1H, s); 8.07 (1H, d)

Step E2: Preparation of *N,N*-Dibenzyl-2-methylamino-3-bromoimidazo[1,2-a]pyridine

20

A mixture of *N,N*-Dibenzyl-2-methylaminoimidazo[1,2-a]pyridine (0.380 g, 1.16 mmol), poly(4-vinylpyridinium tribromide) (0.387 g, 1.16 mmol), pyridine (2 drops) in CH₂Cl₂ (20 mL) were stirred at ambient temperature for 16 h. The solid support was filtered off

and the mother liquors concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, slow gradient, CH₂Cl₂ to 3:7 EtOAc:Hexane to 6:4 EtOAc:Hexane) to yield the title compound as a yellow oil (0.260 g, 55%).

Mass Spectrum: 406, 408 [MH]⁺

5 **¹H NMR spectrum (CDCl₃):** 3.70 (4H, s); 3.82 (2H, s); 6.90 (1H, t); 7.17-7.48 (11H, m);
7.58 (1H, d), 8.08 (1H, d)

Step E3: Preparation of N,N-Dibenzyl-2-methylamino-3-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine

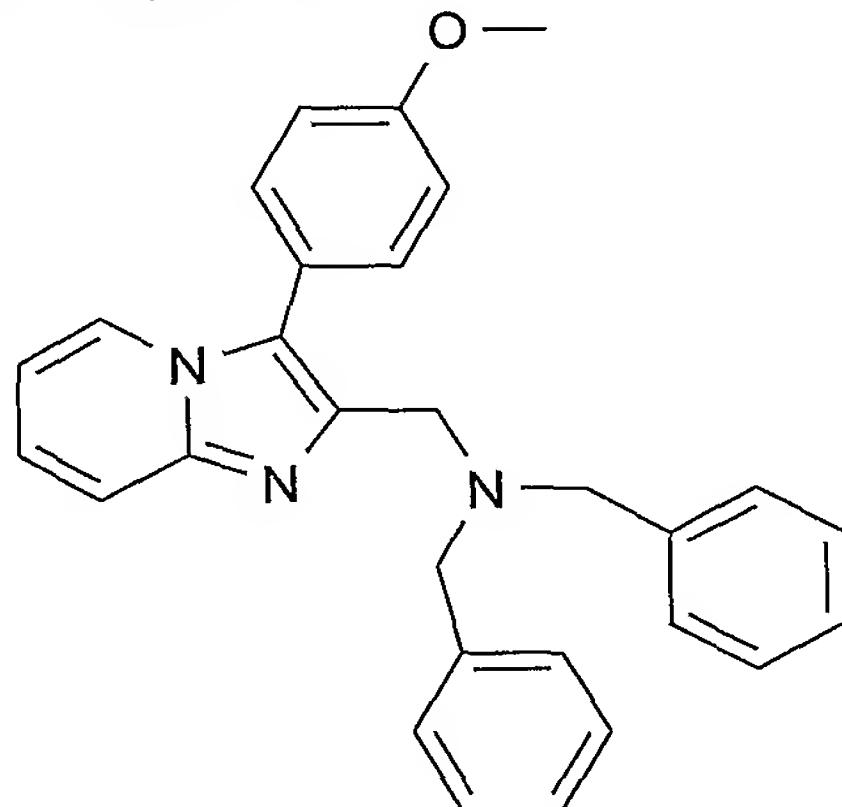
10

To a mixture of *N,N*-Dibenzyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (150 mg, 0.370 mmol), 3,4-dimethoxybenzene boronic acid (81.0 mg, 0.440 mol), saturated Na₂CO₃ (2.5 mL), ethanol (0.90 mL) and toluene (4.50 mL), was added a catalytic amount of Pd(PPh₃)₄. The reaction was stirred at 80 °C for 3 h. The toluene layer was separated and 15 concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient, neat CH₂Cl₂ to 3:7EtOAc:Hexane to 7:3 EtOAc:Hexane) gave the title compound as an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to a solution of the compound in EtOAc to give the title compound dihydrochloride as a white solid (98.0 mg, 49%).

20 **Mass Spectrum:** 464 [MH]⁺

¹H NMR spectrum (DMSO-d₆): 3.75 (3H, s); 3.88 (3H, s); 4.08 (4H, br s); 4.15 (2H, brs); 7.05-7.19 (3H, m); 7.30 (7H, s); 7.46 (4H, s); 7.84 (1H, t); 8.00 (1H, d); 8.43 (1H, d)

Example F - Preparation of *N,N*-Dibenzyl-2-methylamino-3-(4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine

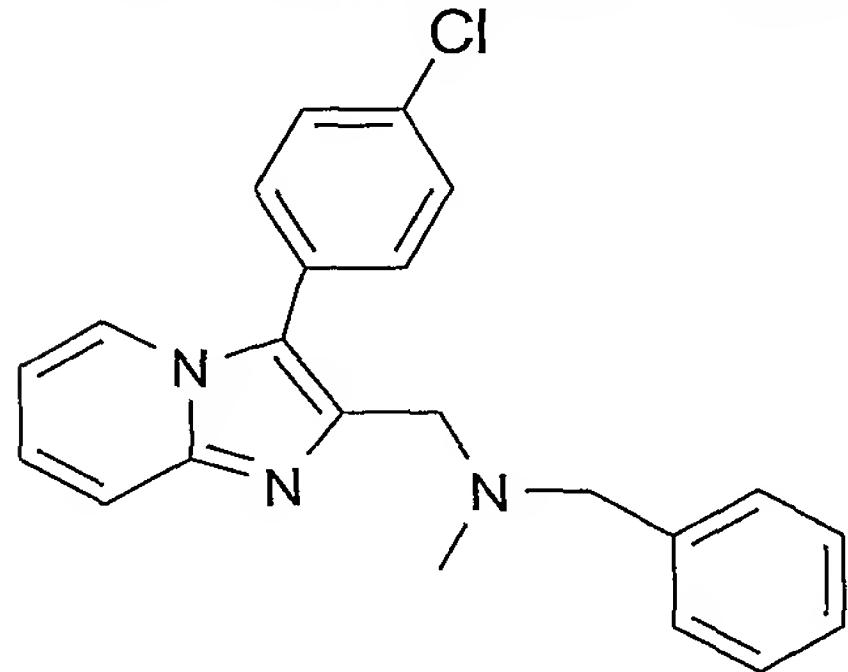


To a mixture of *N,N*-Dibenzyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (100mg, 0.25mmol), 4-methoxybenzene boronic acid (76.0 mg, 0.500 mol), saturated Na₂CO₃ (1.5 mL), ethanol (0.6 mL) and toluene (3 mL), was added a catalytic amount of Pd(PPh₃)₄. The reaction was stirred at 80 °C for 3 h.

The toluene layer was separated and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient, neat CH₂Cl₂ to 3:7 EtOAc:Hexane to 7:3 EtOAc:Hexane) gave the title compound as an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to a solution of the compound in EtOAc to give the title compound dihydrochloride as a white solid (41.0 mg, 32%)

Mass Spectrum: 434 [MH]⁺

Example G - Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine



5 **Step G1: Preparation of 2-chloromethylimidazo[1,2-*a*]pyridine**

A mixture of dichloroacetone (17.8 g, 14.0 mmol) and 2-aminopyridine (10.0 g , 11.0 mmol) in DMF (80 mL) was stirred at ambient temperature for 5 h. The resulting precipitate was filtered off and washed with DMF and then diethyl ether. This solid was 10 then taken up in DMF (100 mL), 4A molecular sieves added and the reaction stirred at 80 °C for 3 h. The resulting precipitate was filtered off and washed with diethyl ether to yield the title compound as a white solid.

Mass Spectrum: 167 [MH]⁺

¹H NMR spectrum (DMSO-d₆): 5.11 (2H, s); 7.48 (1H, t); 7.95 (2H, s); 8.49 (1H, s); 15 8.97 (1H, d).

· **Step G2: Preparation of *N*-benzyl-*N*-methyl-2-methylaminoimidazo[1,2-*a*]pyridine**

20 A mixture of 2-chloromethylimidazo[1,2-*a*]pyridine (2.00 g, 12.0 mmol), *N*-methylbenzylamine (1.75 g, 14.5 mmol) and powdered K₂CO₃ (3.30 g, 2.40 mmol) in DMF (50 mL) was heated at 90 °C for 4 h. After cooling, the inorganics were filtered off and the filtrate evaporated *in vacuo*. Purification by flash column chromatography (silica gel,

slow gradient, CH₂Cl₂ to 5% MeOH:CH₂Cl₂) gave the title compound as a yellow oil (1.42 g, 48%).

Mass Spectrum: 252 [MH]⁺

¹H NMR spectrum (DMSO-d₆): 2.30 (3H, s); 3.63 (2H, s); 3.79 (2H, s); 6.73 (1H, t);

5 7.11 (1H, t); 7.20-7.42 (5H, m); 7.55 (1H, s); 7.57 (1H, d); 8.06 (1H,d)

Step G3: Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine

10 A mixture of *N*-benzyl-*N*-methyl-2-methylaminoimidazo[1,2-*a*]pyridine (1.30 g, 5.20 mmol), poly(4-vinylpyridinium tribromide) (1.82 g, 5.50 mmol) and pyridine (2 drops) in CH₂Cl₂ (20 mL) were stirred at ambient temperature for 16 h. A further portion of poly (4-vinylpyridinium tribromide) (0.400 g, 1.20 mmol) was added and the reaction stirred for a further 16 h. DMF was added, the solid support filtered off, and the mother liquors 15 concentrated *in vacuo*. The residue was triturated with diethyl ether, and filtered to yield the title compound as a cream solid (1.85 g, 99%).

Mass Spectrum: 330, 332 [MH]⁺

¹H NMR spectrum (DMSO-d₆): 2.77 (3H, s); 4.39 (2H, s); 4.43 (2H, br s); 7.16 (1H, t);

20 7.42-7.50 (4H, m); 7.55-8.00 (2H, m); 7.69 (1H, d); 8.40 (1H, d)

20

Step G4: Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine

To a mixture of *N*-benzyl-*N*-methyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (200 mg, 0.60 mmol), 4-chlorobenzeneboronic acid (141 mg, 0.910 mmol) and saturated

25 Na₂CO₃ (3 mL) in ethanol (1.2 mL) and toluene (6 mL) was added a catalytic amount of Pd(PPh₃)₄. The reaction was stirred at 80 °C for 16 h. The reaction was poured onto a

hydromatrix column and eluted with CH₂Cl₂. Flash column chromatography (silica gel,

slow gradient, neat CH₂Cl₂ to 5% MeOH:CH₂Cl₂) gave an oil. The HCl salt was prepared

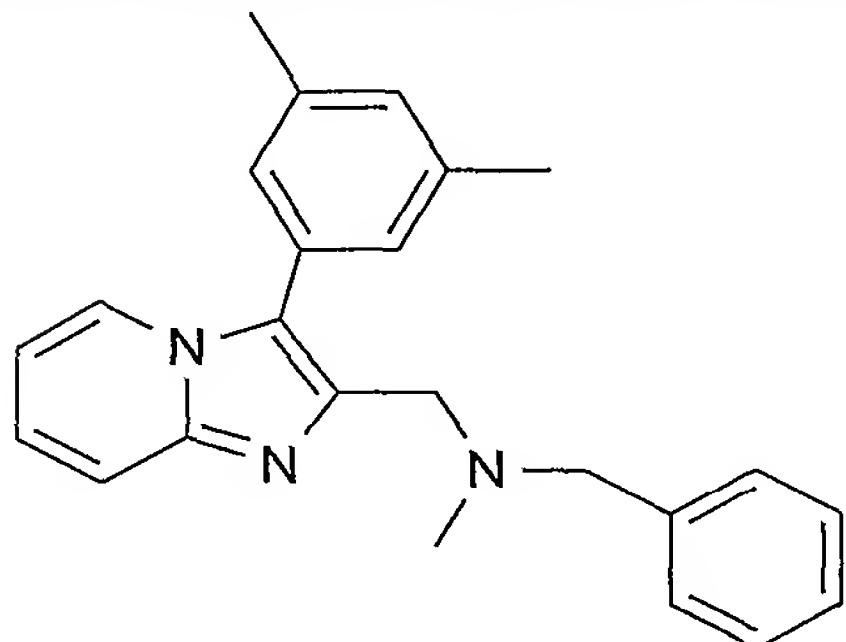
28 by addition of 1M HCl in diethyl ether to a solution of the compound in EtOAc to give the

30 title compound as the dihydrochloride as a white solid (26mgs, 10%).

Mass Spectrum: 362 [MH]⁺

¹H NMR spectrum (DMSO-d₆): 2.72 (3H, s); 4.28 (2H, brs); 4.38 (2H, s); 7.18 (1H, t); 7.35-7.41 (3H, m); 7.50-7.57 (2H, m); 7.63 (5H ,s); 7.51 (1H, d); 8.34 (1H,d)

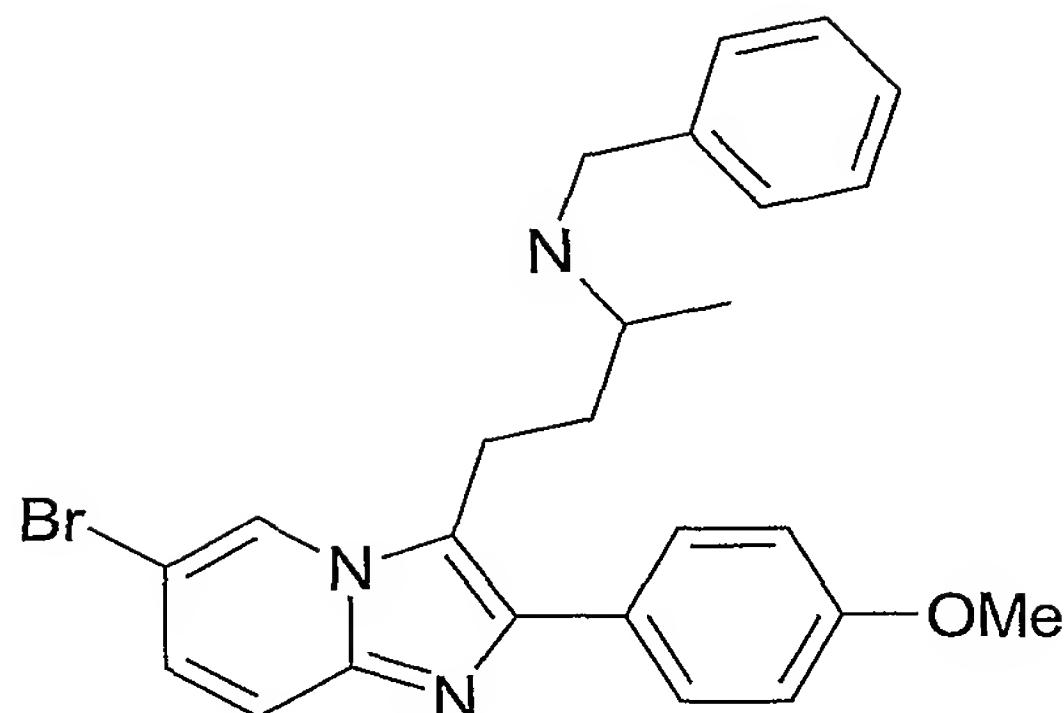
5 **Example H: Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-(3,5-dimethylphenyl)imidazo[1,2-*a*]pyridine**



To a mixture of *N*-benzyl-*N*-methyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (100 mg, 0.400 mmol), 3,5-dimethylbenzene boronic acid (89.0 mg, 0.600 mmol), and sodium carbonate (2 mL) in dioxan (4 mL) was added a catalytic amount of Pd(PPh₃)₄. The reaction was stirred at 90 °C for 16 h, then evaporated *in vacuo*. Purification by flash column chromatography (silica gel, slow gradient, neat CH₂Cl₂ to 5% MeOH:CH₂Cl₂) gave an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to give the title compound dihydrochloride as a white solid (50.0 mg, 29%).

15 Mass Spectrum: 356 [MH]⁺

Example J: Preparation of *N*-Benzyl-5-bromo-3-(3-methylpropylamino)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine



Step J1: 5-bromo-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine

5 2-amino-5-bromopyridine (5.00 g, 28.9 mmol) was added to a solution of 2-bromo-4-methoxyacetophenone (6.62 g, 28.9 mmol) in DMF (50 mL), and the reaction stirred at 80 °C for 2h. The reaction mixture was partitioned between 1M NaOH (200 mL) and ethyl acetate (200 mL), upon which the majority of the product precipitated from solution and was filtered under vacuum. The organic layer that remained was extracted, dried over magnesium sulfate and evaporated *in vacuo* to give a yellow solid, which was combined with the above to give the title compound (6.74 g, 77%).

10 **¹H NMR spectrum (DMSO-d₆):** 3.80 (s, 3H); 7.00 (d, 2H); 7.30 (d, 1H); 7.50 (d, 1H); 7.85 (d, 2H); 8.25 (s, 1H); 8.80 (s, 1H).

15 **Mass Spectrum:** 303, 305 [MH]⁺

15

Step J2: 5-bromo-3-(3-oxo-butyl)-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine

Methyl vinyl ketone (1.00 mL, 12.0 mmol) was added to a solution of 5-bromo-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine (1.00 g 3.32 mmol) in glacial acetic acid (30 mL), followed by the addition of acetic anhydride (10 mL). The reaction was stirred at reflux for 14h. The reaction mixture was evaporated *in vacuo* and the crude product purified by flash chromatography (silica gel, eluting from 25% ethyl acetate:hexane to 50% ethyl acetate:hexane) to give the title compound as a yellow solid (1.09 g, 88%).

¹H NMR spectrum (DMSO-d₆): 2.10 (s, 3H); 2.85 (t, 2H); 3.10 (t, 2H); 3.80 (s, 3H); 7.00 (d, 2H); 7.25 (d, 1H); 7.50 (d, 1H); 7.65 (d, 2H); 8.70 (s, 1H).

Mass Spectrum: 373, 375 [MH]⁺

5

Step J3: *N*-Benzyl-5-bromo-3-(3-methylpropylamino)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

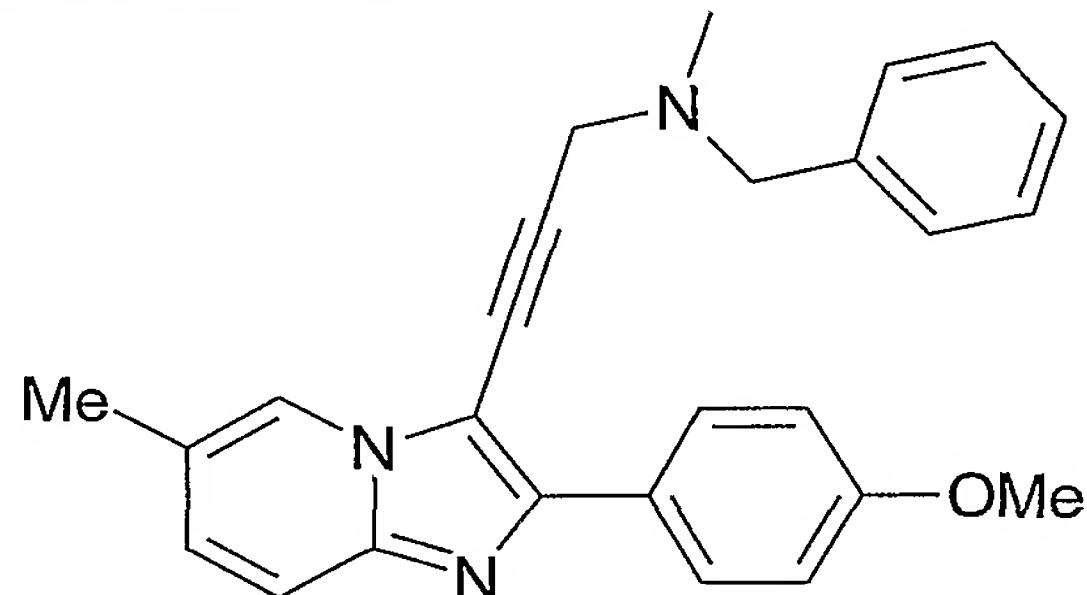
Under an inert atmosphere, benzylamine (0.090 mL, 0.820 mmol) was added to a solution
10 of 5-bromo-3-(3-oxo-butyl)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (300 mg, 0.810 mmol) and toluene sulphonic acid (1 mg, catalytic amount) in anhydrous methanol (10 mL). The reaction mixture was then allowed to reflux over molecular sieves for 16 h. Sodium borohydride (61.0 mg, 1.61 mmol) was added over a period of 30 min, and the reaction left to stir for 30 min. The reaction mixture was evaporated *in vacuo*, and purified
15 by flash chromatography (silica gel, eluting with 1% MeOH: CH₂Cl₂ to 5% MeOH: CH₂Cl₂) to give the title compound as an oil. The hydrochloride salt was formed by addition of HCl in ether, and recrystallised from iso-propanol, to give the title compound hydrochloride as a white solid (40.0 mg, 11%).

¹H NMR spectrum (DMSO-d₆): 1.35 (d, 3H); 1.80-2.00 (m, 2H); 2.15-2.25 (m, 2H);
20 3.75 (q, 1H); 3.85 (s, 3H); 4.00-4.20 (m, 2H); 7.15 (d, 2H); 7.40 (m, 3H); 7.55 (m, 2H); 7.70 (d, 2H); 7.85-8.00 (dd, 2H); 9.20 (s, 1H); 9.45 (s, 1H).

Mass Spectrum: 464, 466 [MH]⁺

25

Example K1: Preparation of N-Benzyl-N-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine



5 **Step K1: 5-methyl-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine**

2-amino-5-picoline (5.00 g, 46.3 mmol) was added to a solution of 2-bromo-4-methoxyacetophenone (10.6 g, 46.3 mmol) in DMF (50 mL), and the reaction stirred at 80 °C for 2h. The reaction mixture was partitioned between 1M NaOH (200 mL) and ethyl acetate (200 mL), upon which the majority of the product precipitated from solution and was filtered under vacuum. The organic layer that remained was extracted, dried over magnesium sulfate and evaporated *in vacuo* to give a yellow solid, which was combined with the above to give the title compound (8.20 g, 74%).

10 **¹H NMR spectrum (DMSO-d₆):** 2.25 (s, 3H); 3.80 (s, 3H); 6.95 (d, 2H); 7.05 (d, 1H); 7.40 (d, 1H); 7.85 (d, 2H); 8.15 (s, 1H); 8.25 (s, 1H).

15 **Mass Spectrum:** 239 [MH]⁺

Step K2: 5-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine

20

Poly(4-vinylpyridinium tribromide) (2.80 g, 8.40 mmol) was added to a solution of 5-methyl-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine (2.00 g, 8.40 mmol) in dichloromethane, which was followed by the addition of a few drops of pyridine. The reaction was allowed to stir at room temperature for 14h. The reaction mixture was filtered by vacuum, washed with water (2 × 75 mL) and the organics separated, dried over

magnesium sulfate, filtered and evaporated *in vacuo* to give the title compound as a pale yellow solid (1.64 g, 62%).

¹H NMR spectrum (DMSO-d₆): 2.25 (s, 3H); 3.80 (s, 3H); 6.95 (d, 2H); 7.05 (d, 1H); 7.40 (d, 1H); 7.85 (d, 2H); 8.15 (s, 1H).

5 **Mass Spectrum:** 317, 319 [MH]⁺

Step K3: *N*-Benzyl-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

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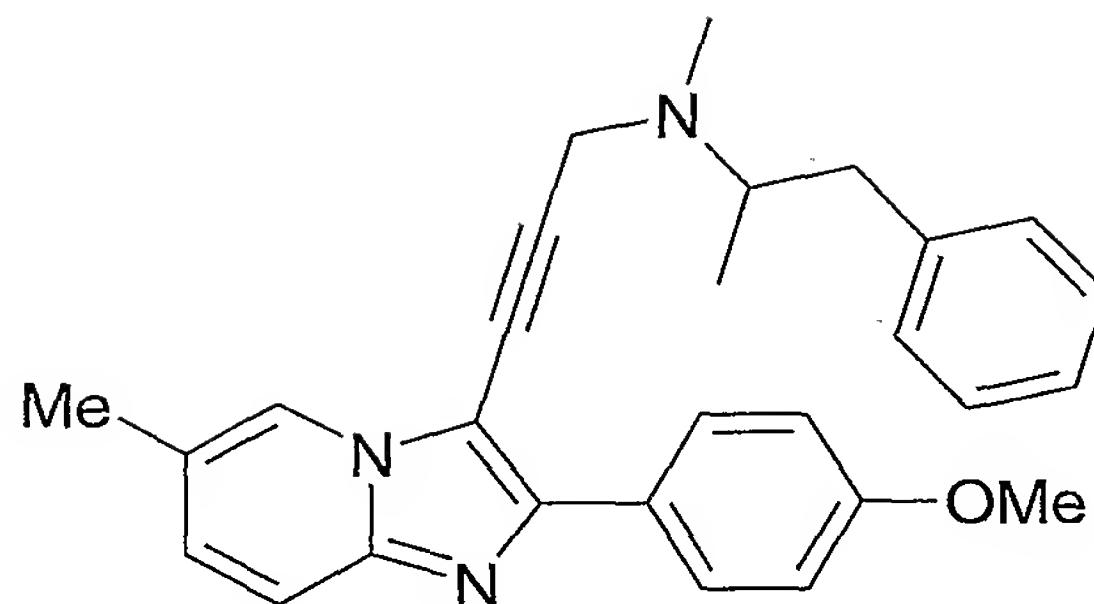
Pargyline hydrochloride (202 mg, 1.26 mmol) was added to a solution of 5-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (20mg, 0.63mmol) in diethylamine (15 mL), and the solution bubbled with nitrogen. Copper Iodide (12.0 mg, 0.060 mmol) was added followed by the addition of bis(triphenylphosphine)palladium dichloride (22.0 mg, 0.030 mmol), and the solution again bubbled with nitrogen. The reaction was then stirred at reflux for 3h, and then at 55 °C for 10 h. The reaction mixture was added to water (50 mL) and extracted with dichloromethane (2 × 50 mL). The organics were dried over magnesium sulfate, filtered, evaporated *in vacuo* and purified by flash chromatography (silica gel, eluting from 10% ethyl acetate:hexane to 40% ethyl acetate:hexane) to give the product and the hydrochloride salt was formed with HCl/ether to give the title compound as an off white solid (37.0 mg, 14%).

¹H NMR spectrum (CDCl₃): 2.40 (s, 3H); 2.50 (s, 3H); 3.75 (s, 2H); 3.80 (s, 2H); 3.85 (s, 3H); 7.00 (d, 2H); 7.10 (d, 1H); 7.25-7.70 (m, 6H); 8.10 (s, 1H); 8.30 (d, 2H).

Mass Spectrum: 396 [MH]⁺

25

Example K2: Preparation of *N*-(β-methylphenethyl)-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

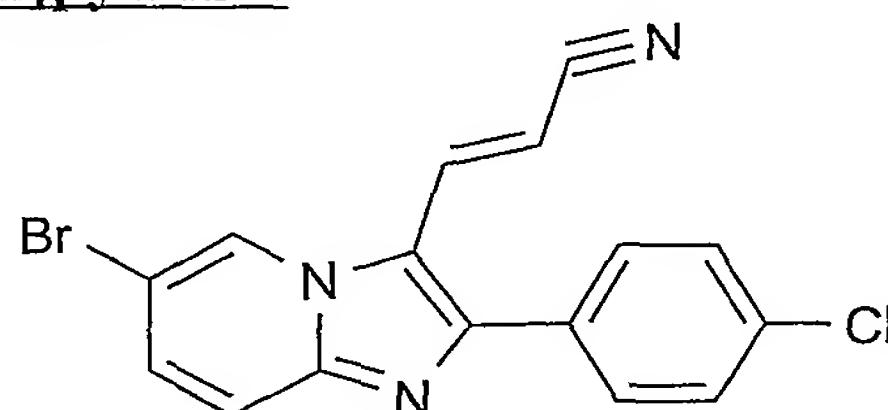


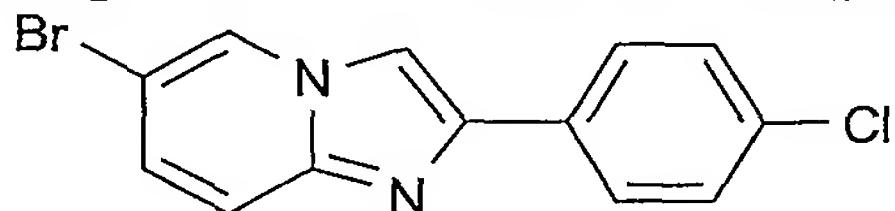
L-Deprenyl (592 mg, 3.16 mmol) was added to a solution of 5-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (500 mg, 1.58 mmol), and the reaction bubbled 5 with nitrogen. Copper iodide (600 mg, 0.320 mmol) and bis(triphenylphosphine)palladium dichloride (110 mg, 0.160 mmol) were added, and the reaction stirred at reflux for 24h. The reaction mixture was partitioned between water (75 mL) and dichloromethane (75 mL), the organics extracted, dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography (silica gel, eluting with 10 30% EtOAc:Hexane to 80% EtOAc:Hexane) to give an oil. The hydrochloride salt was formed by addition of HCl/ether to give the title compound dihydrochloride as a yellow solid (63mg, 9%).

¹H NMR spectrum (DMSO-d₆): 1.20 (m, 3H); 2.40 (s, 3H); 2.75 (m, 1H); 2.95 (s, 3H); 3.45 (s, 2H); 3.80 (s, 3H); 4.70 (m, 2H); 7.00 (d, 2H); 7.20-7.65 (m, 7H); 8.20 (d, 2H); 15 8.70 (s, 1H).

Mass Spectrum: 424 [MH]⁺

Example L: Preparation of 5-bromo-3-(2*E*-cyanoethenyl)-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine



Step L1: 5-bromo-2-(4-chlorophenyl)imidazo[1,2-a]pyridine

2-amino-5-bromopyridine (3.00 g, 17.3 mmol) was added to a solution of 2-bromo-4-chloroacetophenone (4.02 g, 17.3 mmol) in DMF (30 mL), and the reaction stirred at 80 °C for 2 h. The reaction mixture was partitioned between a 1:1 mixture of water and sodium bicarbonate (200 mL) and ethyl acetate (200 mL), upon which the majority of the product precipitated from solution and was filtered under vacuum. The organic layer that remained was extracted, dried over magnesium sulfate and evaporated *in vacuo* to give an off-white solid, which was combined with the above to give the title compound (2.43 g, 46%).

10 ¹H NMR spectrum (CDCl₃): 7.10 (d, 2H); 7.40 (m, 1H); 7.50 (d, 1H); 7.80 (s, 1H); 7.85 (d, 2H); 8.25 (s, 1H).

Mass Spectrum: 307, 309 [MH]⁺

Step L2: 5-bromo-3-formyl-2-(4-chlorophenyl)imidazo[1,2-a]pyridine

15 Under an inert atmosphere, POCl₃ (0.200 mL, 2.45 mmol) was added dropwise to DMF (9 mL) - keeping the internal temperature at 10-20 °C. The reaction mixture was warmed to room temperature, which was followed by the slow addition of 5-bromo-2-(4-chlorophenyl)imidazo[1,2-a]pyridine (500 mg, 1.64 mmol) as a solid. The reaction was stirred for 12 h at 40 °C. Water was added to the mixture until full precipitation had occurred. The resulting suspension was filtered to give the title compound as a cream solid (440 mg, 81%).

20 ¹H NMR spectrum (DMF-d₆): 7.60 (d, 2H); 7.87 (d, 2H); 7.93 (d, 2H); 9.68 (t, 1H); 10.05 (s, 1H).

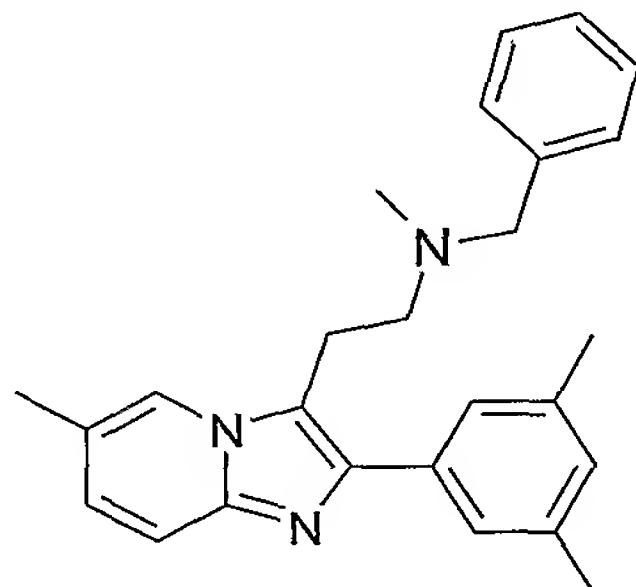
25 Mass Spectrum: 334, 336 [MH]⁺

Step L3: 5-bromo-3-(2E-cyanoethenyl)-2-(4-chlorophenyl)imidazo[1,2-a]pyridine.

At 0 °C, sodium bis(trimethylsilyl)amide (1.0M solution in THF, 1.1 mL, 1.1 mmol) was added to a solution of (cyanomethyl)triphenylphosphoniumchloride (303 mg, 0.900 mmol) in THF, and the reaction allowed to warm to room temperature over 2 h. The reaction was cooled to -78 °C, and 5-bromo-3-formyl-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine (100 mg, 0.300 mmol) in THF was added dropwise. The reaction was stirred at -78 °C→RT for 14h, and for a further 4h at 40 °C. The reaction mixture was partitioned between water and dichloromethane, the organics separated, dried over magnesium sulfate, filtered and evaporated. The crude product was purified by flash chromatography (silica gel, eluting from 10% ethyl acetate/hexane to 50% ethyl acetate/hexane) to give the title compound as an off-white solid (45.0 mg, 42%).

¹H NMR spectrum (DMSO-d₆): 6.15 (d, 1H); 7.50-7.75 (m, 6H); 7.85 (d, 1H); 9.10 (s, 1H)

Example M - Preparation of N-Benzyl-N-methyl-2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-a]pyridine.



5

Step M1: 4-Chloro-2-bromopropyl-3,5-dimethylphenyl ketone.

Pyridinium tribromide (4.56 g 14.3 mmol) was added in one portion to a stirred solution of 4-chloropropyl-3,5-dimethylphenyl ketone (3.00 g 14.3 mmol) [synthesised as described in WO 98/55123] in CH₂Cl₂ (30 mL) at RT and the mixture stirred for 2h. The brown solution was then diluted with ether (200 mL) and washed with 20% NaS₂O₃ (aq) (150 mL), 2M HCl (200 mL) and brine (200 mL). The solution was dried (MgSO₄) and concentrated *in vacuo* to give the crude title compound as a brown oil (4.11 g 99%).

15

Step M2: 2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-a]pyridine.

A mixture of 2-amino-5-methylpyridine (1.08 g 10.0 mmol) and 4-Chloro-2-bromopropyl-3,5-dimethylphenyl ketone (2.90 g 10.0 mmol) in DMF (15 mL) was heated overnight at 80 °C. The mixture was partitioned EtOAc (50 mL) and saturated NaHCO₃ (150mL). The aqueous was extracted with EtOAc (5 × 25 mL) and the combined organics washed with water (25 mL) and brine (25 mL). The solution was dried (MgSO₄) and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient neat *iso*-hexanes to 50% EtOAc) gave the title compound as a yellow gum (610 mg 20%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether to a solution of the

title compound in EtOAc. The salt was precipitated with diethyl ether and collected by centrifuge.

Mass Spectrum: m/e C₁₈H₂₀ClN₂(M+H) 299.16.

5 **¹H NMR spectrum (CDCl₃):** δ ¹H NMR (300 MHz) 2.33 - 2.50 (9H, m), 3.50 - 3.65 (2H, t); 3.70 - 3.80 (2H, t); 6.90 - 7.10 (2H, m); 7.36 (2H, s); 7.55 (1H, d); 7.70 - 7.85 (1H, m).

Step M2: N-Benzyl-N-methyl-2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-a]pyridine.

10

N-Methyl-N-benzylamine (95 μL 0.737 mmol) was added in one portion to a stirred solution of 2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-a]pyridine (200 mg 0.670 mmol) and di-isopropylethylamine (128 mL 0.736 mmol) in DMF (25 mL) was heated overnight at 100 °C. The mixture was partitioned EtOAc (2 × 50 mL) and saturated NaHCO₃ (250 mL) and the combined organics were dried (MgSO₄) and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient neat iso-hexanes to 100% EtOAc) gave the title compound as a yellow gum (135 mg 44%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether to a solution of the title compound in EtOAc. The salt was precipitated with diethyl ether and collected by centrifuge.

20 **Mass Spectrum:** m/e (M+H) 384.67.

25 **¹H NMR spectrum (DMSO-d₆ + CD₃COOD):** δ ¹H NMR (300 MHz) 2.35 (6H, s), 2.75 (3H, s), 3.30 - 3.45 (2H, m); 3.65 - 3.85 (2H, m); 4.20 - 4.50 (2H, m), 7.20 (1H, s); 7.30 (2H, s); 7.35 - 7.45 (3H, m); 7.50 - 7.62 (2H, m); 7.70 - 7.85 (2H, m); 9.05 (1H, s).

THERAPEUTIC USES

Compounds of formulae I and II are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in men and women. To this end, a compound of formulae I and II can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of 0.1mgkg^{-1} to 30mgkg^{-1} (preferably, 5mgkg^{-1} to 20mgkg^{-1}) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

The following illustrate representative pharmaceutical dosage forms containing a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof (hereafter referred to as "compound X"), for use in humans.

5 (a)

<u>Tablet I</u>	<u>mg/tablet</u>
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

<u>Tablet II</u>	<u>mg/tablet</u>
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

10

(c)

<u>Tablet III</u>	<u>mg/tablet</u>
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

<u>Capsule</u>	<u>mg/capsule</u>
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

<u>Injection I</u>	<u>(50 mg/ml)</u>
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

5 Buffers, pharmaceutically acceptable cosolvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostataux, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotropin adenoma.

ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following *in vitro* assays.

5

Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

10

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I -125]D-t-Bu-Ser⁶-Pro⁹-ethyl amide-GnRH, and the test compound. Incubation is at 4°C for 90 minutes to 2 hours.

15

2. Rapidly filter and repeatedly wash through a glass fibre filter.
3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

20 From this data, the IC₅₀ of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%.

Binding Assay Using Human GnRH Receptor

25

Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC₅₀ which is the compound concentration required to inhibit the specific binding of [^{125}I]buserelin to GnRH receptors by 50%. [^{125}I]Buserelin (a peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

Assay to Determine Inhibition of LH release

5 The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

Preparation of Pituitary Glands

10

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS).

15 The glands are further processed by:-

1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
- 20 4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
- 25 6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Resuspension of the cells in culture medium of DMEM containing 0.37% NaHCO₃, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;

9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of 3×10^5 cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being
5 maintained in a humidified 5% CO₂/95% air atmosphere at 37°C for 3 to 4 days

Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the
10 incubation medium.

1.5 hours prior to the assay, the cells are washed three times with DMEM containing
0.37% NaHCO₃, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino
acids (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per
15 ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again
washed twice in this medium .

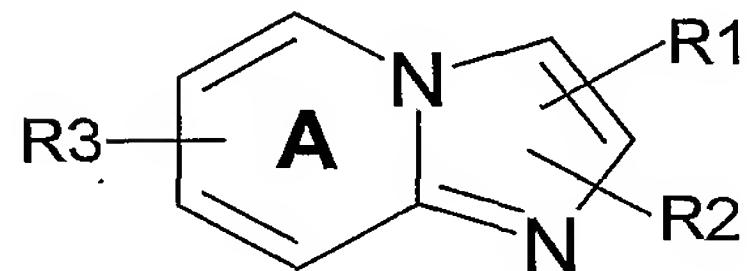
Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is
added to two wells. For other test compounds (where it is desired to test more than one
20 compound), these are added to other respective duplicate wells. Incubation is then carried
out at 37°C for three hours.

Following incubation, each well is analysed by removing the medium from the well and
centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The
25 supernatant is removed and assayed for LH content using a double antibody radio-immuno
assay. Comparison with a suitable control (no test compound) is used to determine
whether the test compound reduces LH release. Compounds according to the present
invention have activity at a concentration from 1nM to 30 µM.

CLAIMS

1. A compound of formula **I** or a pharmaceutically acceptable salt or solvate thereof

5

I

wherein:-

R1 and R2 are independently selected from hydrogen and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom;

R3 is selected from $(CH_2)_a$ -R4, wherein R4 represents an optionally substituted C6 to C14 aryl or an optionally substituted homo- or bi-cyclic heterocyclic ring and a represents zero or an integer from 1 to 5; a group bonded through a heteroatom; an optionally substituted C1 to C20 hydrocarbon residue; optionally substituted C1 to C6 alkyl; C1 to C6 alkyl substituted with a group bonded through a sulphur atom; OR5, wherein R5 represents H or C1 to C6 alkyl; a carbonyl group optionally substituted with a hydrocarbon residue, the residue being optionally substituted; an esterified or amidated carboxyl group; hydrogen; optionally substituted aralkyl; optionally substituted cycloalkyl; and a group of formula W- $(CH_2)_d$, wherein d represents zero or an integer from 1 to 5 and W represents aryl having an optional substituent selected from halogen, nitro, cyano, amino, an optionally substituted carboxyl, alkylenedioxy wherein the alkylene is C1 to C6, and a group of formula -X-R', wherein X represents a chemical bond or a spacer group and R' represents an optionally substituted cycloalkyl or an optionally substituted heterocyclic group; and ring A is optionally further substituted.

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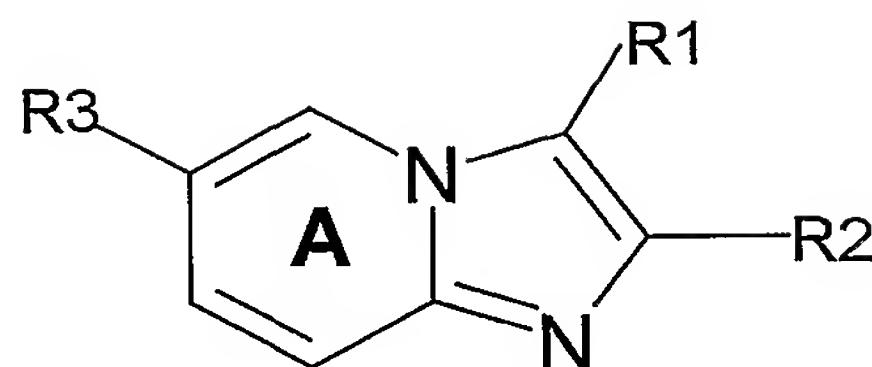
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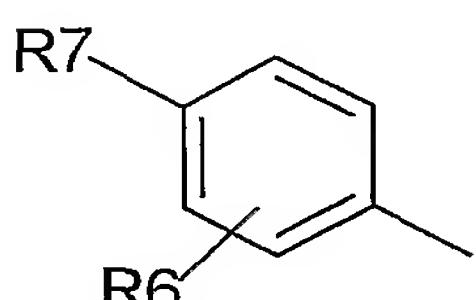
2. The compound of formula **II** or a pharmaceutically acceptable salt or solvate thereof, wherein R1, R2 and R3 are as defined in claim 1

II



3. The compound of claim 1 or 2, wherein R4 represents a group of the formula:-

5



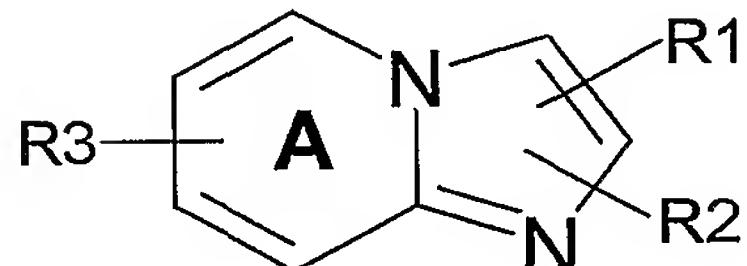
wherein:-

R6 is selected from hydrogen; halogen; and a group bonded through a carbon atom, a
10 nitrogen atom, an oxygen atom or a sulphur atom; and

R7 is selected from hydrogen; halogen; nitro; cyano; and a hydrocarbon residue
optionally substituted by a group bonded through an oxygen atom, a nitrogen atom or a
sulphur atom.

15 4. The compound of any preceding claim, wherein R1 and R2 are independently selected
from a group of the formula $R8-(CH_2)_b-$, wherein each b independently represents zero
or an integer from 1 to 5 and each R8 represents a group bonded through a nitrogen
atom; a group of the formula $R9-B'$ -, wherein R9 is an optionally substituted phenyl
and B' is a chemical bond or spacer group; $R10-(CH_2)_c-$, wherein R10 is an optionally
20 substituted amino and c is zero or an integer from 1 to 5; an optionally substituted C6
to C14 aryl; an optionally substituted C1 to C20 hydrocarbon residue; and optionally
substituted C1 to C6 alkyl.

5. A compound of formula **Ia** or a pharmaceutically acceptable salt or solvate thereof, wherein

Ia

5

wherein:-

R1 and R2 are independently selected from hydrogen and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom;

10 R3 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; C1 to C3 perfluoroalkyl; CN; NO₂; halogen; or R₁₁O(CH₂)_e⁻;

15 wherein R₁₁ represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R₁₂, R₁₃ and R₁₄, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R₁₂, R₁₃ and R₁₄;

20

For R₁₂, R₁₃ and R₁₄, either:-

(a) R₁₂, R₁₃ and R₁₄ independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; (CH₂)_fS(O)_gR₁₅; or halogen; or

(b) R₁₂ meets the definition in (a) and R₁₃ and R₁₄ together represent a 3C to 7C carbocyclic ring or a heterocyclic ring comprising from 1 to 3 heteroatoms selected from O, N and S;

5 R₁₅ represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

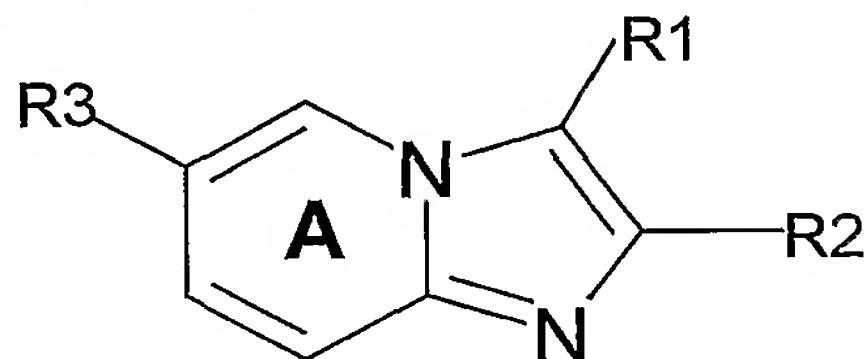
e and f independently represent 0, 1, 2, 3, 4 or 5; and

g represents 0, 1 or 2.

10 and ring A is optionally further substituted.

6. The compound of formula IIa or a pharmaceutically acceptable salt or solvate thereof, wherein R₁, R₂ and R₃ are as defined in claim 5

IIa



15
7. The compound of claim 5 or 6, wherein ring A has a further substituent selected from halogen and -Q(R₁₆)R₁₇, wherein:-

Q represents N; O; S(O)_h; C(O); (CR₁₈R₁₉)_i; a single bond to R₁₆; optionally substituted C2 to C6 alkenyl; or optionally substituted C2 to C6 alkynyl; with the proviso that when Q is O; S(O)_h; C(O); (CR₁₈R₁₉)_i; or a single bond, R₁₇ is absent; and

For R₁₆ and R₁₇, either:-

25 (c) R₁₆ represents hydrogen or optionally substituted C1 to C6 alkyl; and

R₁₇ represents hydrogen; C(O)NR₁₈R₁₉; C(O)R₂₀; NR₁₈R₁₉; C(O)R₁₈;

NR₁₉C(O)R₁₈; NR₁₉C(O)NR₁₈R₁₉; NR₁₉S(O)₂R₁₈; NR₁₉S(O)₂NR₁₈R₁₉;

OC(O)R18; OC(O)NR18R19; OR18; S(O)_jR18; S(O)_jNR18R19; a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21, R22 and R23, or being optionally substituted by an optionally substituted C1 to C6 alkyl; or

5 (d) the structure -Q(R16)R17 represents a heterocyclic ring comprising one or more heteroatoms selected from O, N and S and optionally substituted by R21, R22 and R23; or

(e) the structure -Q(R16)R17 represents a 3-7 membered carbocyclic ring or =O;

10 For R18 and R19, either:-

(f) Each R18 and R19 independently represents a bond; hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21, R22 and R23, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R21, R22 and R23; or

15 (g) R18 and R19 together form part of an optionally substituted 3 to 9-membered ring;

20

R20 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; or optionally substituted aralkyl;

25 For R21, R22 and R23, either:-

(h) Each R21, R22 and R23 independently represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; R18O(CH₂)_k, where R18 meets the definition in section (f); (CH₂)_kS(O)_jR24; or halogen; or

30

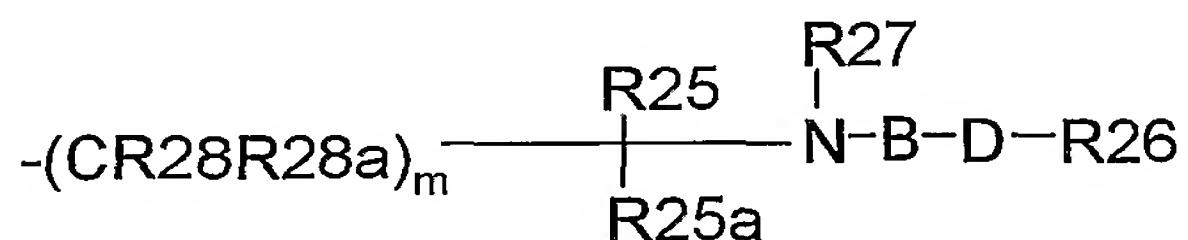
(i) R21 is as defined in section (h) and R22 and R23 together represent a C3 to C7 carbocyclic ring or a heterocyclic ring containing from 1 to 3 heteroatoms selected from O, N and S;

5 R24 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

i and k independently represent 0, 1, 2, 3, 4 or 5; and each h, j and l independently represent 0, 1 or 2.

10

8. The compound of claim 1, 2, 3, 5, 6 or 7, wherein R1 represents the group



15

wherein:-

B represents R29-Y-R29, wherein Y represents optionally substituted aryl;

D is selected from a bond; -OR29-; -C(=O)R29-; -S(O)_nR29-; -NR29R30-; -OC(=O)R29-; -C(=O)OR29-; -NR31C(=O)R29-; -C(=O)NR31R29-; -OS(O)_nR29-; -S(O)_nOR29-; and -NR31S(O)_nR29-;

20

For R25, R25a, R27, R28 and R28a either:-

(i) R25, R25a, R27, R28 and R28a are independently selected from hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; and optionally substituted aralkyl;

25

(j) R25 and R25a together represent a 3-7 membered carbocyclic ring or =O; and R27, R28 and R28a meet the definition in section (i);

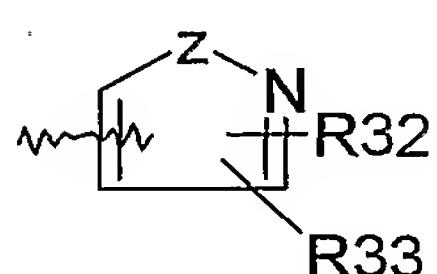
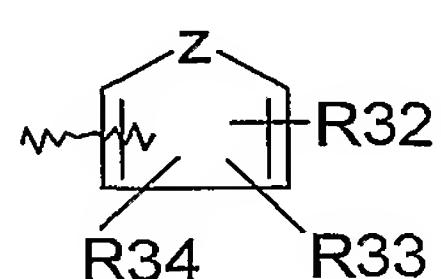
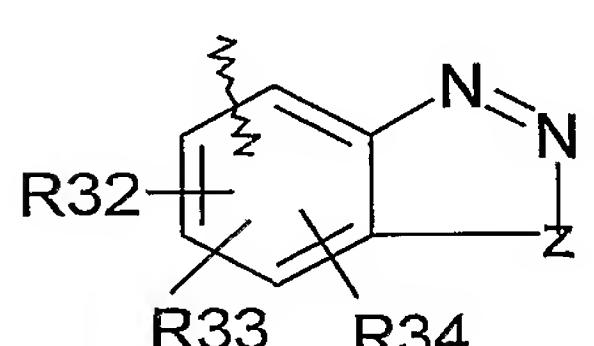
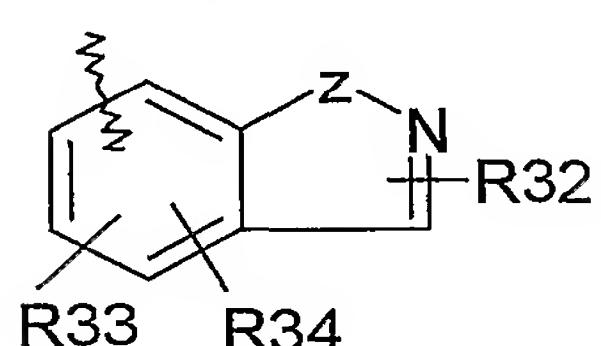
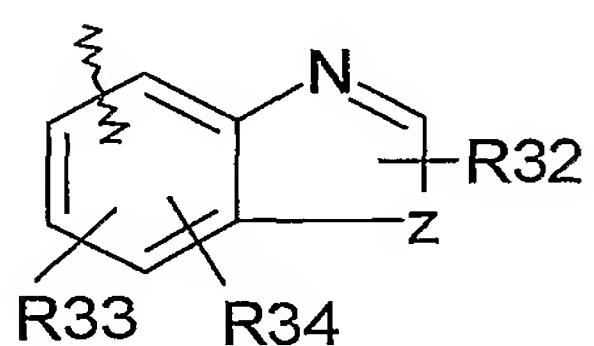
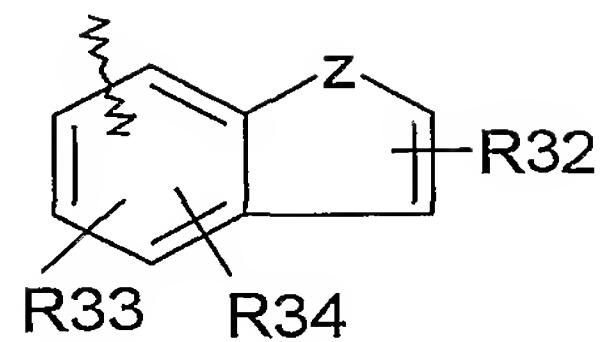
(k)R25, R25a and R27 meet the definition in section (i); and R28 and R28a together represent a 3-7 membered carbocyclic ring or =O;

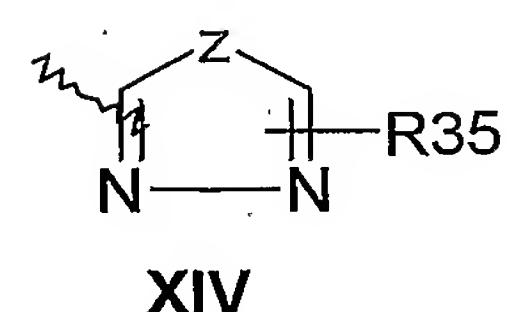
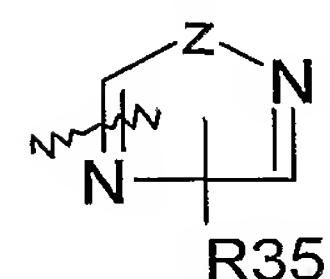
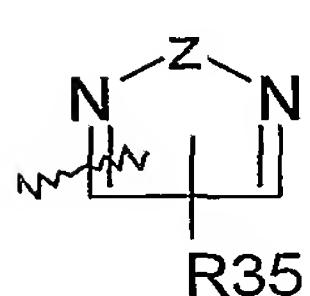
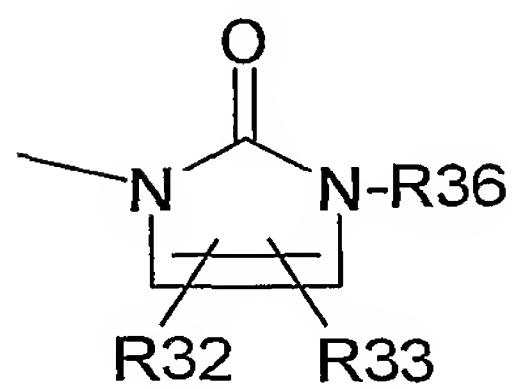
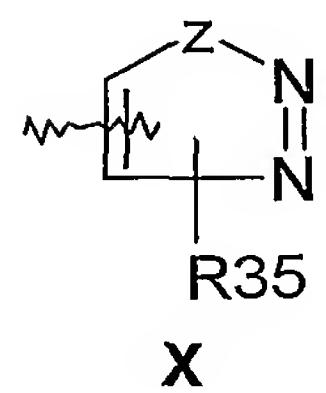
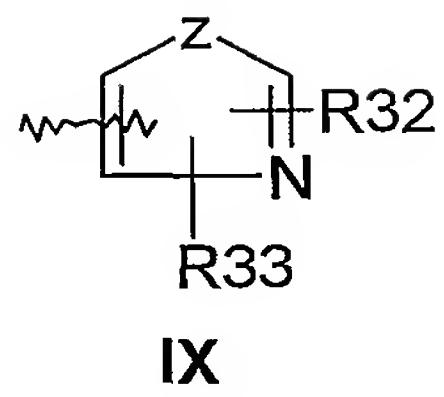
5 (l) R25 and R28 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25a, R27 and R28a meet the definition in section (i);

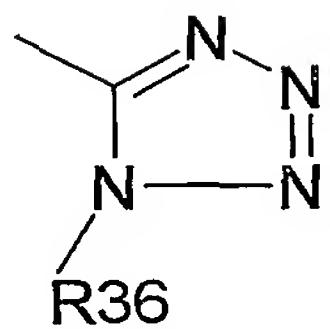
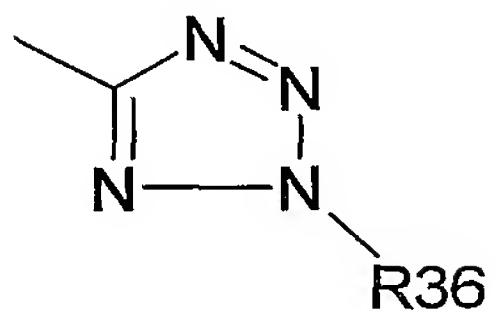
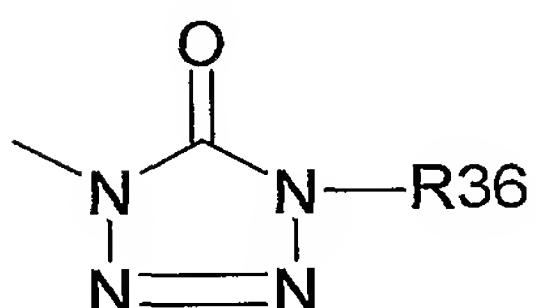
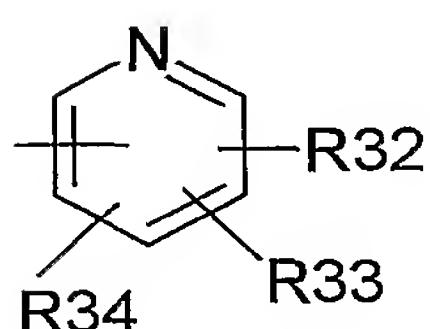
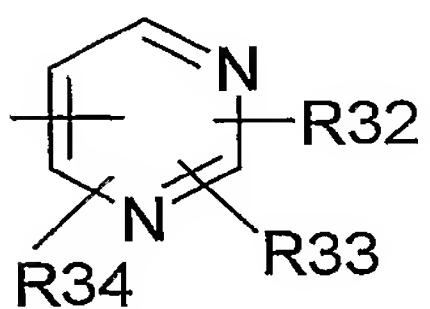
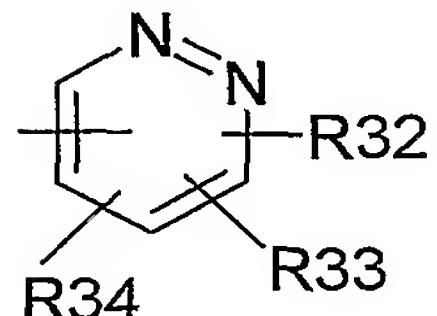
10 (m) R27 and R28 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25, R25a and R28a meet the definition in section (i); or

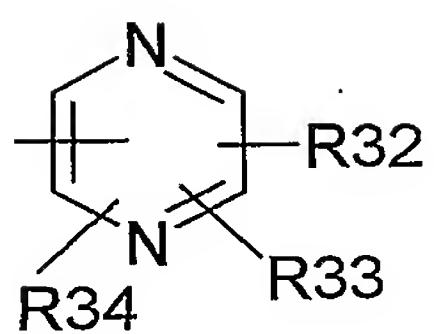
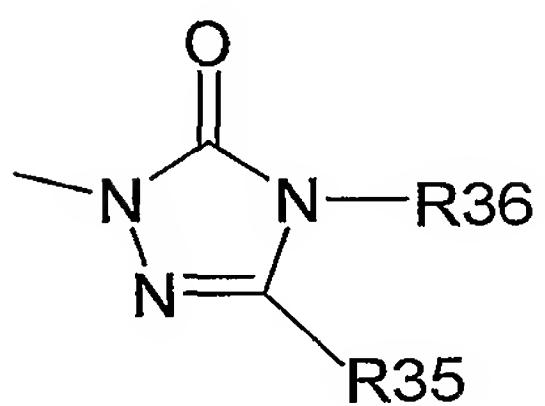
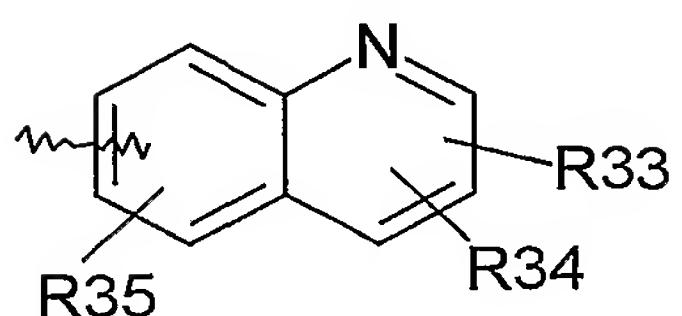
15 (n)R25 and R27 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25a, R28 and R28a meet the definition in section (i);

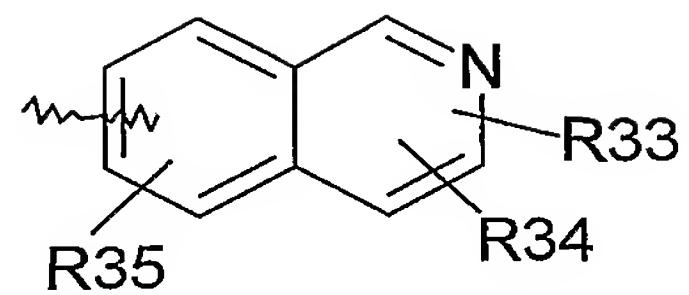
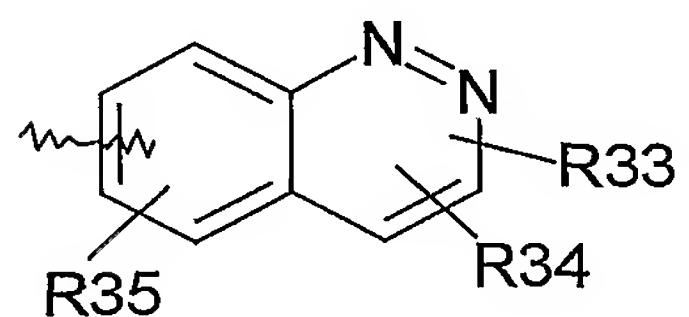
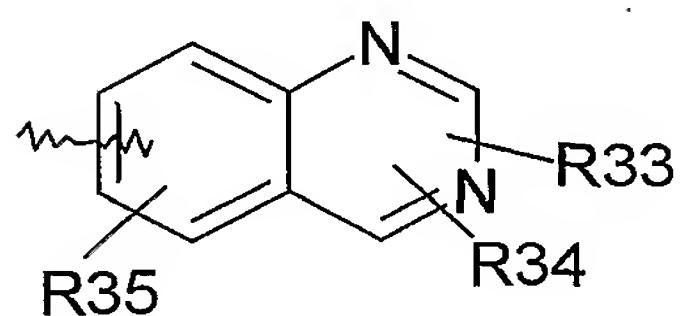
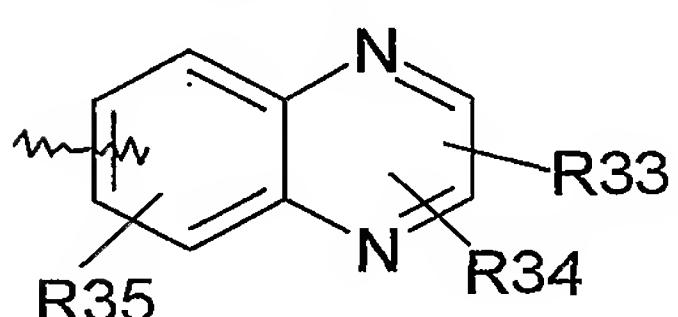
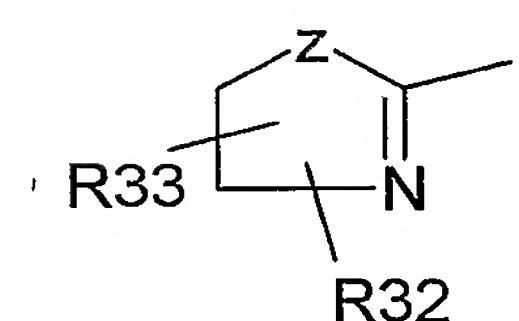
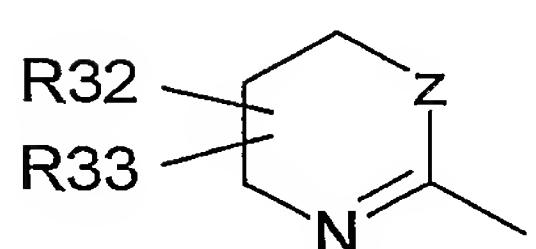
R26 represents a substituent selected from **III** to **XXIX** or an N-oxide thereof:-





**XV****XVI****XVII****XVIII****XIX****XX**

**XXI****XXII****XXIII**

**XXIV****XXV****XXVI****XXVII****XXVIII****XXIX**

Each R29 is independently selected from a bond and optionally substituted C1 to C4 alkyl;

5 R30 represents hydrogen; optionally substituted C1 to C6 alkyl; C(O)OR37; C(O)N(R37)₂; C(O)R37; or S(O)_oR37;

10 R31 and R36 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R38, R39 and R40, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R38, R39 and R40;

15 R32 represents hydrogen; OH; NR41R42; NR37SO₂(optionally substituted C1 to C6 alkyl); NR37SO₂(optionally substituted aryl); NR37SO₂(C1 to C3 perfluoroalkyl); SO₂NR37(optionally substituted C1 to C6 alkyl);
20 SO₂NR37(optionally substituted aryl); SO₂NR37(C1 to C3 perfluoroalkyl); SO₂NR37(C(O)-optionally substituted C1 to C6 alkyl); SO₂NR37(C(O)-optionally substituted aryl); S(O)_p(optionally substituted C1 to C6 alkyl); S(O)_p(optionally substituted aryl); C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted C1 to C6 alkoxy; COOH; halogen; NO₂; or CN;

25 R33 and R34 are independently selected from hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; R37O(CH₂)_q⁻; R37C(O)O(CH₂)_q⁻;

R₃₇OC(O)(CH₂)_q-; -(CH₂)_qS(O)_rR'; where R' is hydrogen, optionally substituted C1 to C6 alkyl, C1 to C3 perfluoroalkyl or optionally substituted aryl; -(CH₂)_qC(O)N(R₃₇)₂; or halogen;

5 R₃₅ meets a definition of either R₃₂ or R₃₃;

Each R₃₇ independently represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; or an optionally substituted 3 to 7-membered carbocyclic ring;

10 R₃₈, R₃₉ and R₄₀ independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; (CH₂)_sS(O)_tR₄₃; or halogen;

15 For R₄₁ and R₄₂, either:-
(o) R₄₁ represents hydrogen or optionally substituted C1 to C6 alkyl; and
R₄₂ represents hydrogen; C(O)NR_{18'}R_{19'}; C(O)R_{20'}; NR_{18'}R_{19'};
C(O)R_{18'}; NR_{19'}C(O)R_{18'}; NR_{19'}C(O)NR_{18'}R_{19'}; NR_{19'}S(O)₂R_{18'};
NR_{19'}S(O)₂NR_{18'}R_{19'}; OC(O)R_{18'}; OC(O)NR_{18'}R_{19'}; OR_{18'};
S(O)_uR_{18'}; S(O)_uNR_{18'}R_{19'}; a mono- or bi-cyclic heterocyclic ring
20 comprising from 1 to 4 heteroatoms selected from O, N and S and being
optionally substituted by R_{21'}, R_{22'} and R_{23'}, or being optionally
substituted by an optionally substituted C1 to C6 alkyl; wherein R_{18'},
R_{19'}, R_{20'}, R_{21'}, R_{22'} and R_{23'} meet a definition respectively of R₁₈,
R₁₉, R₂₀, R₂₁, R₂₂ and R₂₃ in claim 7; or

25 (p) the structure -N(R₄₁)R₄₂ represents a heterocyclic ring comprising one or
more heteroatoms selected from O, N and S and optionally substituted by
R_{21'}, R_{22'} and R_{23'}; wherein R_{21'}, R_{22'} and R_{23'} meet a definition
30 respectively of R₂₁, R₂₂ and R₂₃ in claim 7;

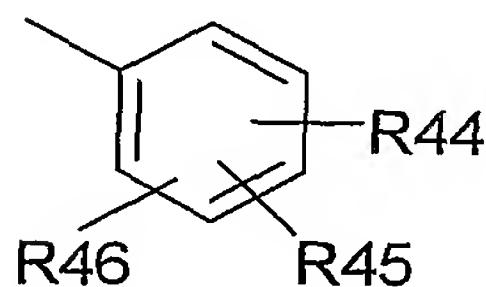
R43 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

5 Z represents O, S or NR18';

R18' meets a definition of R18 in section (f) of claim 7;

10 Each m, q and s independently represent 0, 1, 2, 3, 4 or 5; and
n, o, p, r, t and u independently represent 0, 1 or 2.

9. The compound of any one of claims 1 to 3, 5, 6, 7 and 8, wherein R2 represents a substituent of formula XXX:-



15 **XXX**

R44, R45 and R46 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl;
20 $(CH_2)_vS(O)_wR47$; or halogen;

R47 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

25 v represents 0, 1, 2, 3, 4 or 5; and

w represents 0, 1 or 2.

10. The compound of claim 1, wherein the compound is selected from

2-{2-(3,5-Dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-N,N-diisobutyl-isobutyramide;

2-(3,5-Dimethyl-phenyl)-3-{2-[(5-pyridin-3-yl-thiophen-2-ylmethyl)-amino]-ethyl}-imidazo[1,2-a]pyridine-6-carboxylic acid diisopropylamide;

10 1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-3-yl-benzylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-2-methyl-propan-1-one;

15 1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-benzylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-2-methyl-propan-1-one;

1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-(2-(3,5-dimethyl-phenyl)-3-{(R)-1-methyl-2-[2-(3-methyl-3H-imidazo[4,5-b]pyridin-6-yl)-ethylamino]-ethyl}-imidazo[1,2-a]pyridin-6-yl)-2-methyl-propan-1-one;

20 2-(2-(3,5-dimethyl-phenyl)-3-{(R)-2-[2-(4-methanesulfonylamino-phenyl)-ethylamino]-1-methyl-ethyl}-imidazo[1,2-a]pyridin-6-yl)-N,N-diisobutyl-isobutyramide;

25 2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-N,N-diethyl-isobutyramide;

2-(3,5-dimethyl-phenyl)-3-{2-(4-pyridin-4-yl-butylamino)-ethyl}-imidazo[1,2-a]pyridine-6-carboxylic acid diethylamide;

30 Benzyl-[2-(4-methoxyphenyl)-6-oxazol-4-yl-imidazo[1,2-a]pyridin-3-ylmethyl]-methylamine;

Propane-2-sulfonic acid 3-[(benzylmethylamino)-methyl]-2-[4-(2-methylpropanoylamino)-phenyl]-imidazo[1,2-a]pyridin-6-yl ester;

5 3-[(Benzylmethylamino)-methyl]-2-(4-methoxyphenyl)-imidazo[1,2-a]pyridine-6-carboxylic acid ethyl ester;

2-(4-Acetylaminophenyl)-3-[(benzylmethylamino)-methyl]-imidazo[1,2-a]pyridine-6-carboxylic acid ethyl ester;

10 N-{4-[3-(Benzylmethylamino)-methyl]-6-(2-methylpropanoyl)-imidazo[1,2-a]pyridin-2-yl}-phenyl}-isobutyramide;

N-{4-[3-(Benzylmethylamino)-methyl]-6-(1-phenylmethanoyl)-imidazo[1,2-a]pyridin-2-yl}-phenyl}-isobutyramide;

15 3-[(Benzylmethylamino)-methyl]-2-[4-(2-methyl-propanoylamino)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropyl ester;

20 3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid benzylmethylamide;

3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropylamide; or

25 3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropylmethylamide;

or a pharmaceutically acceptable salt or solvate thereof.

11. A compound according to any preceding claim for use as a medicament.

12. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable diluent or carrier.

13. Use of a compound according to any one of claims 1 to 10, in the manufacture of a composition, for antagonising gonadotropin releasing hormone activity.

14. Use of a compound according to any one of claims 1 to 10, in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinising hormone by the pituitary gland of the patient.

10

15. Use of a compound according to any one of claims 1 to 10, in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

15

16. The use according to claim 15, wherein the sex hormone related condition is selected from a sex hormone dependent cancer, benign prostatic hypertrophy or myoma of the uterus.

20

17. The use according to claim 16, wherein the sex hormone dependent cancer is selected from prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrope adenoma.

25

18. A method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering to the patient a compound according to any one of claims 1 to 10.

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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report

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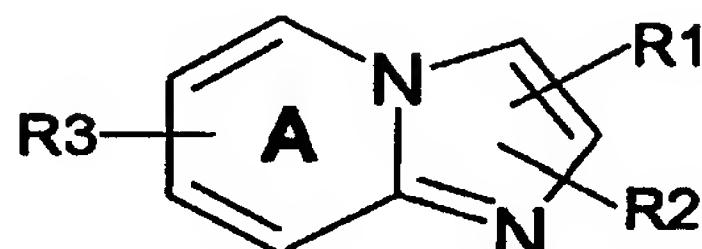
(88) Date of publication of the international search report:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: IMIDAZOPYRIDINES



(I)

defined in the description; and ring A is optionally further substituted.

(57) Abstract: The present invention relates to compounds of formula I which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds wherein: - R1, R2 and R3 are as

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/00634

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/437 A61P5/00 A61P35/00
 //((C07D471/04, 235:00, 221:00))

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 41252 A (MERCK) 19 August 1999 (1999-08-19) claims 1-7; examples 1G,1I ---	1,12-17
X	WO 99 41251 A (MERCK) 19 August 1999 (1999-08-19) claims 1-7; examples 1Q,1S,1U,1W, ---	1,12-17
X	WO 99 20223 A (NOVONORDISK) 29 April 1999 (1999-04-29) claims 1, 3 and 8 (E 1020) ---	1,12,14, 15
X	WO 98 03505 A (TAKEDA) 29 January 1998 (1998-01-29) page 134; claims 1,13,14; examples 120,136 ---	1,12,17 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

11 July 2002

Date of mailing of the international search report

26/07/2002

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Alfarro Faus, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/00634

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 19953 A (ASTA MEDICA) 5 June 1997 (1997-06-05) claims 1,17; example 28 ---	1,12, 14-17
P,X	WO 01 55119 A (NEUROCRINE) 2 August 2001 (2001-08-02) page 132 -page 134; claims 1,39-42; example 12 ---	1,12,13, 15-17
P,X	WO 01 83481 A (IMP CANCER RES TECHNOLOGY) 8 November 2001 (2001-11-08) abstract page 29 -page 43 ---	1,12,16
X	KAMINSKI J J ET AL: "JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 28, no. 7, 1985, pages 876-892, XP002094814 ISSN: 0022-2623 tables 3,4 -----	1,12

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/GB 02/00634

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1-12 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search is only complete for the use of the compounds of claim 1 according to claims 13 to 18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

— Information on patent family members

International Application No

PCT/GB 02/00634

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